METHODS FOR MOLECULAR TOXICOLOGY MODELING

INVENTORS: James C. DIGGANS and Michael ELASHOFF

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Ser. No. 60/554,981, filed March 22, 2004 and U.S. Provisional Application Ser. No. 60/613,831, filed September 29, 2004, both of which are herein incorporated by reference in their entirety for all purposes. This application also claims priority to PCT Application No. PCT/US03/37556, filed November 24, 2003, which is herein incorporated by reference in its entirety for all purposes.

SEQUENCE LISTING SUBMISSION ON COMPACT DISC

[0002] The Sequence Listing submitted concurrently herewith on compact disc under 37 C.F.R. §§1.821(c) and 1.821(e) is herein incorporated by reference in its entirety. Four copies of the Sequence Listing, one on each of four compact discs are provided. Copy 1, Copy 2 and Copy 3 are identical. Copies 1, 2 and 3 are also identical to the CRF. Each electronic copy of the Sequence Listing was created on November 22, 2004 with a file size of 2398 KB. The file names are as follows: Copy 1- gene logic 5133-wo.txt; Copy 2- gene logic 5133-wo.txt; Copy 3- gene logic 5133-wo.txt; CRF- gene logic 5133-wo.txt.

BACKGROUND OF THE INVENTION

[0003] The need for methods of assessing the toxic impact of a compound, pharmaceutical agent or environmental pollutant on a cell or living organism has led to the development of procedures which utilize living organisms as biological monitors. The simplest and most convenient of these systems utilize unicellular microorganisms such as yeast and bacteria, since they are the most easily maintained and manipulated. In addition, unicellular screening systems often use easily detectable changes in phenotype to monitor the effect of test compounds on the cell. Unicellular organisms, however, are inadequate models for estimating the potential effects of many compounds on complex multicellular animals, as they do not have the ability to carry out biotransformations.

[0004] The biotransformation of chemical compounds by multicellular organisms is a significant factor in determining the overall toxicity of agents to which they are exposed.

Accordingly, multicellular screening systems may be preferred or required to detect the toxic effects of compounds. The use of multicellular organisms as toxicology screening tools has been significantly hampered, however, by the lack of convenient screening mechanisms or endpoints, such as those available in yeast or bacterial systems. Additionally, certain previous attempts to produce toxicology prediction systems have failed to provide the necessary modeling data and statistical information to accurately predict toxic responses (*e.g.*, WO 00/12760, WO 00/47761, WO 00/63435, WO 01/32928, and WO 01/38579).

[0005] The pharmaceutical industry spends significant resources to ensure that therapeutic compounds of interest are not toxic to human beings. This process is lengthy as well as expensive and involves testing in a series of organisms starting with rats and progressing to dogs or non-human primates. Moreover, modeling methods for designing candidate pharmaceuticals and their synthesis in nucleic acid, peptide or organic compound libraries has increased the need for inexpensive, fast and accurate methods to predict toxic responses. Toxicity modeling methods based on nucleic acid hybridization platforms would allow the use biological samples from compound-exposed animal or cell culture samples, such as rats or rat hepatocyte cell cultures, to detect human organ toxicity much earlier than has been possible to date.

SUMMARY OF THE INVENTION

[0006] The present invention is based, in part, on the elucidation of the global changes in gene expression in animal tissues or cells, such as liver or kidney tissue or cells, exposed to known toxins, in particular hepatotoxins or renal toxins, as compared to unexposed tissues or cells, as well as the identification of individual genes that are differentially expressed upon toxin exposure.

[0007] In various aspects, the invention includes methods of predicting at least one toxic effect of a test agent by comparing gene expression information from agent-exposed samples to a database of gene expression information from toxin-exposed and control samples (vehicle-exposed samples or samples exposed to a non-toxic compound or low levels of a toxic compound). These methods comprise providing or generating quantitative gene expression information from the samples, converting the gene expression information to matrices of fold-change values by a robust multi-array average (RMA) algorithm, generating

a gene regulation score for each gene that is differentially expressed upon exposure to the test agent by a partial least squares (PLS) algorithm, and calculating a sample prediction score for the test agent. This sample prediction score is then compared to a reference prediction score for one or more toxicity models. If the sample prediction score is equal to or greater than the reference prediction score, the test agent can be predicted to have at least one toxic effect or to produce at least one pathology corresponding to the toxicity model to which the test agent's prediction score is compared.

[0008] In various aspects, the invention includes methods of creating a toxicology model. These methods comprise providing or generating quantitative nucleic acid hybridization data for a plurality of genes from at least one cell or tissue sample exposed to a toxin and at least one cell or tissue sample exposed to the toxin vehicle, converting the hybridization data from at least one gene to a gene expression measure, such as fold-change value, by a robust multi-array average (RMA) algorithm, generating a gene regulation score from a gene expression measure for at least one gene by a partial least squares (PLS) algorithm, and generating a toxicity reference prediction score for the toxin, thereby creating a toxicology model.

[0009] In other aspects, the invention includes a computer system comprising a computer readable medium containing a toxicity model for predicting the toxicity of a test agent and software that allows a user to predict at least one toxic effect of a test agent by comparing a sample prediction score for the test agent to a toxicity reference prediction score for the toxicity model.

[0010] In further aspects of the invention, the gene expression information from test agent-exposed tissues or cells may be prepared as text or binary files, such as CEL files, and transmitted via the Internet for analysis and comparisons to the toxicity models stored on a remote, central server. After processing, the user that sent the text files receives a report indicating the toxicity or non-toxicity of the test agent.

[0011] In other aspects of the invention, the user may download one or more toxicity models from the remote, central server, as well as software for manipulating the user's data and the toxicity models, to a local server. Gene expression information from test agent-exposed tissues or cells may then be prepared as text files, such as CEL files, and analyzed and compared at the user's site to the toxicity models stored on the local server. After processing, the software generates a report indicating the toxicity or non-toxicity of the test agent.

TABLES

[0012] Table 1: Table 1 provides the GLGC identifier (fragment names from Table 2) in relation to the SEQ ID NO. and GenBank Accession number for each of the gene fragments listed in Table 2 (all of which are herein incorporated by reference and replication in the attached sequence listing). The gene names and Unigene cluster titles are also included.

[0013] Table 2: Table 2 presents the PLS scores (weighted gene index scores) from an exemplary kidney general toxicity model.

DETAILED DESCRIPTION

Definitions

[0014] As used herein, "nucleic acid hybridization data" refers to any data derived from the hybridization of a sample of nucleic acids to a one or more of a series of reference nucleic acids. Such reference nucleic acids may be in the form of probes on a microarray or set of beads or may be in the form of primers that are used in polymerization reactions, such as PCR amplification, to detect hybridization of the primers to the sample nucleic acids. Nucleic hybridization data may be in the form of numerical representations of the hybridization and may be derived from quantitative, semi-quantitative or non-quantitative analysis techniques or technology platforms. Nucleic acid hybridization data includes, but is not limited to gene expression data. The data may be in any form, including florescence data or measurements of florescence probe intensities from a microarray or other hybridization technology platform. The nucleic acid hybridization data may be raw data or may be normalized to correct for, or take into account, background or raw noise values, including background generated by microarray high/low intensity spots, scratches, high regional or overall background and raw noise generated by scanner electrical noise and sample quality fluctuation.

[0015] As used herein, "cell or tissue samples" refers to one or more samples comprising cell or tissue from an animal or other organism, including laboratory animals such as rats or mice. The cell or tissue sample may comprise a mixed population of cells or tissues or may be substantially a single cell or tissue type, such as hepatocytes or liver tissue. Cell or tissue samples as used herein may also be *in vitro* grown cells or tissue, such as primary cell cultures, immortalized cell cultures, cultured hepatocytes, cultured liver tissue, etc.. Cells or

tissue may be derived from any organ, including but not limited to, liver, kidney, cardiac, muscle (skeletal or cardiac) or brain.

[0016] As used herein, "test agent" refers to an agent, compound or composition that is being tested or analyzed in a method of the invention. For instance, a test agent may be a pharmaceutical candidate for which toxicology data is desired.

[0017] As used herein, "test agent vehicle" refers to the diluent or carrier in which the test agent is dissolved, suspended in or administered in, to an animal, organism or cells.

[0018] As used herein, "toxin vehicle" refers to the diluent or carrier in which a toxin is dissolved, suspended in or administered in, to an animal, organism or cells.

[0019] As used herein, a "gene expression measure" refers to any numerical representation of the expression level of a gene or gene fragment in a cell or tissue sample. A "gene expression measure" includes, but is not limited to, a fold-change value.

[0020] As used herein, "at least one gene" refers to a nucleic acid molecule detected by the methods of the invention in a sample. The term "gene" as used herein, includes fully characterized open reading frames and the encoded mRNA as well as fragments of expressed RNA that are detectable by any hybridization method in the cell or tissue samples assayed as described herein. For instance, a "gene" includes any species of nucleic acid that is detectable by hybridization to a probe in a microarray, such as the "genes" of Table 1. As used herein, at least one gene includes a "plurality of genes."

[0021] As used herein, "fold-change value" refers to a numerical representation of the expression level of a gene, genes or gene fragments between experimental paradigms, such as a test or treated cell or tissue sample, compared to any standard or control. For instance, a fold-change value may be presented as microarray-derived florescence or probe intensities for a gene or genes from a test cell or tissue sample compared to a control, such as an unexposed cell or tissue sample or a vehicle-exposed cell or tissue sample. An RMA fold-change value as described herein is a non-limiting example of a fold-change value calculated by methods of the invention.

[0022] As used herein, "gene regulation score" refers to a quantitative measure of gene expression for a gene or gene fragment as derived from a weighted index score or PLS score for each gene and the fold-change value from treated vs. control samples.

[0023] As used herein, "sample prediction score" refers to a numerical score produced via methods of the invention as herein described. For instance, a "sample prediction score" may

be calculated using the PLS weight or PLS score for at least one gene in a gene expression profile generated from the sample and the RMA fold-change value for that same gene. A "sample prediction score" is derived from summing the individual gene regulation scores calculated for a given sample.

[0024] As used herein, "toxicity reference prediction score" refers to a numerical score generated from a toxicity model that can be used as a cut-off score to predict at least one toxic effect of a test agent. For instance, a sample prediction score can be compared to a toxicity reference prediction score to determine if the sample score is above or below the toxicity reference prediction score. Sample prediction scores falling below the value of a toxicity reference prediction score are scored as not exhibiting at least one toxic effect and sample prediction scores above the value if a toxicity reference prediction score are scored as exhibiting at least one toxic effect.

[0025] As used herein, a log scale linear additive model includes any log-liner model such as log scale robust multi-array average or RMA (Irizarry *et al.*, Nucleic Acids Research 31(4) e15 (2003).

[0026] As used herein, "remote connection" refers to a connection to a server by a means other than a direct hard-wired connection. This term includes, but is not limited to, connection to a server through a dial-up line, broadband connection, Wi-Fi connection, or through the Internet.

[0027] As used herein, a "CEL file" refers to a file that contains the average probe intensities associated with a coordinate position, cell or feature on a microarray (such information provided by the CDF or 1LQ file). See Affymetrix GeneChip® Expression Analysis Technical Manual, which is herein

[0028] As used herein, a "gene expression profile" comprises any quantitative representation of the expression of at least one mRNA species in a cell sample or population and includes profiles made by various methods such as differential display, PCR, microarray and other hybridization analysis, *etc.*

Methods of Generating Toxicity Models

[0029] To evaluate and identify gene expression changes that are predictive of toxicity, studies using selected compounds with well characterized toxicity may be used to build a model or database of the present invention. Methods of the present invention include an

RMA/PLS method (analysis of raw gene expression data by the robust multi-array average algorithm, with evaluation of predictive ability by the partial least squares algorithm) to create models and databases for predicting toxicity.

[0030] In general, cell and tissue samples are analyzed after exposure to compounds known to exhibit at least one toxic effect. Low doses of these compounds, or the vehicles in which they were prepared, are used as negative controls. Compounds that are known not to exhibit at least one toxic effect may also be used as negative controls.

[0031] In the present invention, a toxicity study or "tox study" comprises a set of cell or tissue samples that have been exposed to one or more toxins and may include matched samples exposed to the toxin vehicle or a low, non-toxic, dose of the toxin. As described below, the cell or tissue samples may be exposed to the toxin and control treatments *in vivo* or *in vitro*. In some studies, toxin and control exposure to the cell or tissue samples may take place by administering an appropriate dose to an animal model, such as a laboratory rat. In some studies, toxin and control exposure to the cell or tissue samples may take place by administering an appropriate dose to a sample of *in* vitro grown cells or tissue, such as primary rat or human hepatocytes. These samples are typically organized into cohorts by test compound, time (for instance, time from initial test compound dosage to time at which rats are sacrificed), and dose (amount of test compound administered). All cohorts in a tox study typically share the same vehicle control. For example, a cohort may be a set of samples from rats that were treated with acyclovir for 6 hours at a high dosage (100 mg/kg). A time-matched vehicle cohort is a set of samples that serve as controls for treated animals within a tox study, *e.g.*, for 6-hour acyclovir-treated high dose samples the time-matched vehicle cohort would be the 6-hour vehicle-treated samples with that study.

[0032] A toxicity database or "tox database" is a set of tox studies that alone or in combination comprise a reference database. For instance, a reference database may include data from rat tissue and cell samples from rats that were treated with different test compounds at different dosages and exposed to the test compounds for varying lengths of time.

[0033] RMA, or robust multi-array average, is an algorithm that converts raw fluorescence intensities, such as those derived from hybridization of sample nucleic acids to an Affymetrix GeneChip® microarray, into expression values, one value for each gene fragment on a chip (Irizarry *et al.* (2003), *Nucleic Acids Res.* 31(4):e15, 8 pp.; and Irizarry *et al.* (2003) "Exploration, normalization, and summaries of high density oligonucleotide array probe level

data," *Biostatistics* 4(2): 249-264). RMA produces values on a log2 scale, typically between 4 and 12, for genes that are expressed significantly above or below control levels. These RMA values can be positive or negative and are centered around zero for a fold-change of about 1. A matrix of gene expression values generated by RMA can be subjected to PLS to produce a model for prediction of toxic responses, *e.g.*, a model for predicting liver or kidney toxicity. In a preferred embodiment, the model is validated by techniques known to those skilled in the art. Preferably, a cross-validation technique is used. In such a technique, the data is randomly broken into training and test sets several times until model success rate is determined. Most preferably, such technique uses 2/3 / 1/3 cross-validation, where 1/3 of the data is dropped and the other 2/3 is used to rebuild the model.

[0034] PLS, or Partial Least Squares, is a modeling algorithm that takes as inputs a matrix of predictors and a vector of supervised scores to generate a set of prediction weights for each of the input predictors (Nguyen *et al.* (2002), *Bioinformatics* 18:39-50). These prediction weights are then used to calculate a gene regulation score to indicate the ability of each analyzed gene to predict a toxic response. As described in the examples, the gene regulation scores may then be used to calculate a toxicity reference prediction score.

[0035] From the nucleic acid hybridization data, a gene expression measure is calculated for one or more genes whose level of expression is detected in the nucleic acid hybridization value. As described above, the gene expression measure may comprise an RMA fold-change value. The toxicity reference score = $\Sigma\, w_i\, R^{FC_i}$. "i" is the index number for each gene in a gene expression profile to be evaluated. "w_i" is the PLS weight (or PLS score, see Table 2) for each gene. "R^{FC_i}" is the RMA fold-change value for the i^{th} gene, as determined from a normalized RMA matrix of gene expression data from the sample (described above). The PLS weight multiplied by the RMA fold-change value gives a gene regulation score for each gene, and the regulation scores for all the individual genes are added to give a toxicity reference prediction score for a sample or cohort of sample. A toxicity reference prediction score can be calculated from at least one gene regulation score, or at least about 5, 10, 25, 50, 100, 500 or about 1,000 or more gene regulation scores.

[0036] In one embodiment of the invention, a toxicology or toxicity model of the invention is prepared or created by the steps of (a) providing nucleic acid hybridization data for a plurality of genes from at least one cell or tissue sample exposed to a toxin and at least one cell or tissue sample exposed to the toxin vehicle; (b) converting the hybridization data from at least

one gene to a gene expression measure; (c) generating a gene regulation score from gene expression measure for said at least one gene; and (d) generating a toxicity reference prediction score for the toxin, thereby creating a toxicology model. The gene expression measure may be a gene fold-change value calculated by a log scale linear additive model such as RMA and the toxicity reference prediction score may be generated with PLS. The toxicity reference prediction score may then be added to a toxicity model or database and be used to predict at least one toxic effect of an unknown test agent or compound.

[0037] In another preferred embodiment, the model is validated by techniques known to those skilled in the art. Preferably, a cross-validation technique is used. In such a technique, the data is randomly broken into training and test sets several times until an acceptable model success rate is determined. Most preferably, such technique uses 2/3 / 1/3 cross-validation, where 1/3 of the data is dropped and the other 2/3 is used to rebuild the model.

Methods of Predicting Toxic Effects

[0038] The gene regulation scores and toxicity prediction scores derived from cell or tissue samples exposed to toxins may be used to predict at least one toxic effect, including the hepatotoxicity, renal toxicity or other tissue toxicity of a test or unknown agent or compound. The gene regulation scores and toxicity prediction scores from cell or tissue samples exposed to toxins may also be used to predict the ability of a test agent or compound to induce a tissue pathology, such as liver necrosis, in a sample. The toxicology prediction methods of the invention are limited only by the availability of the appropriate toxicology model and toxicology prediction scores. For instance, the prediction methods of a given system, such as a computer system or database of the invention, can be expanded simply by running new toxicology studies and models of the invention using additional toxins or specific tissue pathology inducing agents and the appropriate cell or tissue samples.

[0039] As used, herein, at least one toxic effect includes, but is not limited to, a detrimental change in the physiological status of a cell or organism. The response may be, but is not required to be, associated with a particular pathology, such as tissue necrosis. Accordingly, the toxic effect includes effects at the molecular and cellular level. Hepatotoxicity, for instance, is an effect as used herein and includes but is not limited to the pathologies of: cholestasis, genotoxicity/carcinogenesis, hepatitis, human-specific toxicity, induction of liver enlargement, steatosis, macrovesicular steatosis, microvesicular steatosis, necrosis, non-

genotoxic/non-carcinogenic toxicity, peroxisome proliferation, rat non-genotoxic toxicity, and general hepatotoxicity.

[0040] In general, assays to predict the toxicity of a test agent (or compound or multi-component composition) comprise the steps of exposing a cell or tissue sample or population of cell or tissue samples to the test agent or compound, providing nucleic acid hybridization data for at least one gene from the test agent exposed cell or tissue sample(s), by, for instance, assaying or measuring the level of relative or absolute gene expression of one or more of the genes, such as one or more of the genes in Table 2, calculating a sample prediction score and comparing the sample prediction score to one or more toxicology reference scores (see Example 1).

[0041] Sample prediction scores may be calculated as follows: sample prediction score = Σ $w_i R^{FC_i}$. "i" is the index number for each gene in a gene expression profile to be evaluated. "w_i" is the PLS weight (or PLS score) for each gene derived from a toxicity model. "R^{FC_i}" is the RMA fold-change value for the i^{th} gene, as determined from a normalized RMA matrix of gene expression data from the sample (described above). The PLS weight from a given model multiplied by the RMA fold-change value gives a gene regulation score for each gene, and the regulation scores for all the individual genes are added to give a prediction score for the sample.

[0042] Nucleic acid hybridization data may include any measurement of the hybridization, including gene expression levels, of sample nucleic acids to probes corresponding to about (or at least) 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 50, 75, 100, 200, 500, 1000 or more genes, or ranges of these numbers, such as about 2-10, about 10-20, about 20-50, about 50-100, about 100-200, about 200-500 or about 500-1000 genes. Nucleic acid hybridization data for toxicity prediction may also include the measurement of nearly all the genes in a toxicity model. "Nearly all" the genes may be considered to mean at least 80% of the genes in any one toxicity model.

[0043] The methods of the invention to predict at least one toxic effect of a test agent or compound may be practiced by one individual or at one location, or may be practiced by more than one individual or at more than one location. For instance, methods of the invention include steps wherein the exposure of a test agent or compound to a cell or tissue sample(s) is accomplished in one location, nucleic acid processing and the generation of

nucleic acid hybridization data takes place at another location and gene regulation and sample prediction scores calculated or generated at another location.

[0044] In another embodiment of the invention, cell or tissue samples are exposed to a test agent or compound by administering the agent to laboratory rats and nucleic acids are processed from selected tissues and hybridized to a microarray to produce nucleic acid hybridization data. The nucleic acid hybridization data is then sent to a remote server comprising a toxicology reference database and software that enables generation of individual gene regulation scores and one or more sample prediction scores from the nucleic acid hybridization data. The software may also enable a user to pre-select specific toxicology models and to compare the generated sample prediction scores to one or more toxicology reference scores contained within a database of such scores. The user may then generate or order an appropriate output product(s) that presents or represents the results of the data analysis, generation of gene regulation scores, sample prediction scores and/or comparisons to one or more toxicology reference scores.

[0045] Data, including nucleic acid hybridization data, may be transmitted to a server via any means available, including a secure direct dial-up or a secure or unsecured Internet connection. Toxicology prediction reports or any result of the methods herein may also be transmitted via these same mechanisms. For instance, a first user may transmit nucleic acid hybridization data to a remote server via a secure password protected Internet link and then request transmission of a toxicology report from the server via that same Internet link.

[0046] Data transmitted by a remote user of a toxicity database or model may be raw, un-normalized data or may be normalized from various background parameters before transmission. For instance, data from a microarray may be normalized for various chip and background parameters such as those described above, before transmission. The data may be in any form, as long as the data can be recognized and properly formatted by available software or the software provided as part of a database or computer system. For instance, microarray data may be provided and transmitted in a .cel file or any other common data files produced from the analysis of microarray based hybridization on commercially available technology platforms (see, for instance, the Affymetrix GeneChip® Expression Analysis Technical Manual available at www.affymetrix.com). Such files may or may not be annotated with various information, for instance, but not limited to, information related to the

customer or remote user, cell or tissue sample data or information, hybridization technology or platform on which the data was generated and/or test agent data or information.

[0047] Once data is received, the nucleic acid hybridization data may be screened for database compatibility by any available means. In one embodiment, commonly available data quality control metrics can be applied. For instance, outlier analysis methods or techniques may be utilized to identify samples incompatible with the database, for instance, samples exhibiting erroneous florescence values from control probes which are common between the data and the database or toxicity model. In addition, various data QC metrics can be applied, including one or more disclosed in PCT/US03/24160, filed August 1, 2003, which claims priority to U.S. provisional application 60/399,727.

Cell or Tissue Sample Preparation

[0048] As described above, the cell population that is exposed to the test agent, compound or composition may be exposed *in vitro* or *in vivo*. For instance, cultured or freshly isolated liver cells, in particular rat hepatocytes, may be exposed to the agent under standard laboratory and cell culture conditions. In another assay format, *in vivo* exposure may be accomplished by administration of the agent to a living animal, for instance a laboratory rat.

[0049] Procedures for designing and conducting toxicity tests in *in vitro* and *in vivo* systems are well known, and are described in many texts on the subject, such as Loomis *et al.*, Loomis's Esstentials of Toxicology, 4th Ed., Academic Press, New York, 1996; Echobichon, The Basics of Toxicity Testing, CRC Press, Boca Raton, 1992; Frazier, editor, *In Vitro* Toxicity Testing, Marcel Dekker, New York, 1992; and the like.

[0050] In *in vitro* toxicity testing, two groups of test organisms are usually employed. One group serves as a control, and the other group receives the test compound in a single dose (for acute toxicity tests) or a regimen of doses (for prolonged or chronic toxicity tests). Because, in some cases, the extraction of tissue as called for in the methods of the invention requires sacrificing the test animal, both the control group and the group receiving compound must be large enough to permit removal of animals for sampling tissues, if it is desired to observe the dynamics of gene expression through the duration of an experiment.

[0051] In setting up a toxicity study, extensive guidance is provided in the literature for selecting the appropriate test organism for the compound being tested, route of administration. dose ranges, and the like. Water or physiological saline (0.9% NaCl in water)

is the solute of choice for the test compound since these solvents permit administration by a variety of routes. When this is not possible because of solubility limitations, vegetable oils such as corn oil or organic solvents such as propylene glycol may be used.

[0052] Regardless of the route of administration, the volume required to administer a given dose is limited by the size of the animal that is used. It is desirable to keep the volume of each dose uniform within and between groups of animals. When rats or mice are used, the volume administered by the oral route generally should not exceed about 0.005 ml per gram of animal. Even when aqueous or physiological saline solutions are used for parenteral injection the volumes that are tolerated are limited, although such solutions are ordinarily thought of as being innocuous. The intravenous LD_{50} of distilled water in the mouse is approximately 0.044 ml per gram and that of isotonic saline is 0.068 ml per gram of mouse. In some instances, the route of administration to the test animal should be the same as, or as similar as possible to, the route of administration of the compound to man for therapeutic purposes.

[0053] When a compound is to be administered by inhalation, special techniques for generating test atmospheres are necessary. The methods usually involve aerosolization or nebulization of fluids containing the compound. If the agent to be tested is a fluid that has an appreciable vapor pressure, it may be administered by passing air through the solution under controlled temperature conditions. Under these conditions, dose is estimated from the volume of air inhaled per unit time, the temperature of the solution, and the vapor pressure of the agent involved. Gases are metered from reservoirs. When particles of a solution are to be administered, unless the particle size is less than about 2 μm the particles will not reach the terminal alveolar sacs in the lungs. A variety of apparati and chambers are available to perform studies for detecting effects of irritant or other toxic endpoints when they are administered by inhalation. The preferred method of administering an agent to animals is via the oral route, either by intubation or by incorporating the agent in the feed.

[0054] When the agent is exposed to cells *in vitro* or in cell culture, the cell population to be exposed to the agent may be divided into two or more subpopulations, for instance, by dividing the population into two or more identical aliquots. In some preferred embodiments of the methods of the invention, the cells to be exposed to the agent are derived from liver tissue. For instance, cultured or freshly isolated rat hepatocytes may be used.

[0055] The methods of the invention may be used generally to predict at least one toxic response, and, as described in the Examples, may be used to predict the likelihood that a compound or test agent will induce various specific pathologies, such as liver cholestasis, genotoxicity/carcinogenesis, hepatitis, human-specific toxicity, induction of liver enlargement, steatosis, macrovesicular steatosis, microvesicular steatosis, necrosis, non-genotoxic/non-carcinogenic toxicity, peroxisome proliferation, rat non-genotoxic toxicity, general hepatotoxicity, or other pathologies associated with at least one known toxin. The methods of the invention may also be used to determine the similarity of a toxic response to one or more individual compounds. In addition, the methods of the invention may be used to predict or elucidate the potential cellular pathways influenced, induced or modulated by the compound or test agent.

Databases and Computer Systems

[0056] Databases and computer systems of the present invention typically comprise one or more data structures comprising toxicity or toxicology models as described herein, including models comprising individual gene or toxicology marker weighted index scores or PLS scores (See Table 2), gene regulation scores, sample prediction scores and/or toxicity reference prediction scores. Such databases and computer systems may also comprise software that allows a user to manipulate the database content or to calculate or generate scores as described herein, including individual gene regulation scores and sample prediction scores from nucleic acid hybridization data. Software may also allow a user to predict, assay for or screen for at least one toxic response, including toxicity, hepatotoxicity, renal toxicity, etc, to include gene or protein pathway information and/or to include information related to the mechanism of toxicity, including possible cellular and molecular mechanisms. As an example, software may include at least one element from the Gene Logic ToxShield™ Predictive Modeling System such as software comprising at least one algorithm to convert hybridization data from varying platforms, for instance from one microarray platform to a second microarray platform (see U.S. Provisional Application 60/613,831, filed September 29, 2004, which is herein incorporated by reference in its entirety for all purposes).

[0057] As discussed above, the databases and computer systems of the invention may comprise equipment and software that allow access directly or through a remote link, such as direct dial-up access or access via a password protected Internet link.

[0058] Any available hardware may be used to create computer systems of the invention. Any appropriate computer platform, user interface, *etc.* may be used to perform the necessary comparisons between sequence information, gene or toxicology marker information and any other information in the database or information provided as an input. For example, a large number of computer workstations are available from a variety of manufacturers. Client/server environments, database servers and networks are also widely available and appropriate platforms for the databases of the invention.

[0059] The databases may be designed to include different parts, for instance a sequence database and a toxicology reference database. Methods for the configuration and construction of such databases and computer-readable media containing such databases are widely available, for instance, see U.S. Publication No. 2003/0171876 (Serial No. 10/090,144), filed March 5, 2002, PCT Publication No. WO 02/095659, published November 23, 2002, and U.S. Patent No. 5,953,727, which are herein incorporated by reference in their entirety. In a preferred embodiment, the database is a ToxExpress® or BioExpress® database marketed by Gene Logic Inc., Gaithersburg, MD.

[0060] The databases of the invention may be linked to an outside or external database such as GenBank (*www.ncbi.nlm.nih.gov/entrez.index.html*); KEGG (*www.genome.ad.jp/kegg*); SPAD (*www.grt.kyushu-u.ac.jp/spad/index.html*); HUGO (*www.gene.ucl.ac.uk/hugo*); Swiss-Prot (*www.expasy.ch.sprot*); Prosite (*www.expasy.ch/tools/scnpsit1.html*); OMIM (*www.ncbi.nlm.nih.gov/omim*); and GDB (*www.gdb.org*). In a preferred embodiment, the external database is GenBank and the associated databases maintained by the National Center for Biotechnology Information (NCBI) (*www.ncbi.nlm.nih.gov*).

Toxicity or Toxicology Reports

[0061] As descried above, the methods, databases and computer systems of the invention can be used to produce, deliver and/or send a toxicity or toxicology report. As consistent with the use of the terms "toxicity" and "toxicology" as used herein, a "toxicity report" and a "toxicology report" are interchangeable.

[0062] The toxicity report of the invention typically comprises information or data related to the results of the practice of a method of the invention. For instance, the practice of a method of identifying at least one toxic effect of a test agent or compound as herein described may result in the preparation or production of a report describing the results of the method

including an indication or prediction of at least one toxic response, such as toxicity, hepatotoxicity, renal toxicity, etc. The report may comprise information related to the toxic effects predicted by the comparison of at least one sample prediction score to at least one toxicity reference prediction score from the database as well as other related information such as a literature review or citation list and/or information regarding potential toxicity mechanism(s) of action, etc. The report may also present information concerning the nucleic acid hybridization data, such as the integrity of the data as well as information input by the user of the database and methods of the invention, such as information used to annotate the nucleic acid hybridization data.

[0063] As an exemplary, non-limiting example, a toxicity report of the invention may be in a form such as the reports disclosed in PCT US02/22701, filed July 18, 2002, and U.S. Provisional Application 60/613,831, filed September 29, 2004, both of which are herein incorporated by reference in their entirety for all purposes. As described elsewhere in this specification, the report may be generated by a server or computer system to which is loaded nucleic acid hybridization data by a user. The report related to that nucleic acid data may be generated and delivered to the user via remote means such as a password secured environment available over the Internet or via available computer communication means such as email.

Generating Nucleic Acid Hybridization Data

[0064] Any assay format to detect gene expression may be used to produce nucleic acid hybridization data. For example, traditional Northern blotting, dot or slot blot, nuclease protection, primer directed amplification, RT- PCR, semi- or quantitative PCR, branched-chain DNA and differential display methods may be used for detecting gene expression levels or producing nucleic acid hybridization data. Those methods are useful for some embodiments of the invention. In cases where smaller numbers of genes are detected, amplification based assays may be most efficient. Methods and assays of the invention, however, may be most efficiently designed with high-throughput hybridization-based methods for detecting the expression of a large number of genes.

[0065] To produce nucleic acid hybridization data, any hybridization assay format may be used, including solution-based and solid support-based assay formats. Solid supports containing oligonucleotide probes for differentially expressed genes of the invention can be

filters, polyvinyl chloride dishes, particles, beads, microparticles or silicon or glass based chips, *etc.* Such chips, wafers and hybridization methods are widely available, for example, those disclosed by Beattie (WO 95/11755).

[0066] Any solid surface to which oligonucleotides can be bound, either directly or indirectly, either covalently or non-covalently, can be used. A preferred solid support is a high density array or DNA chip. These contain a particular oligonucleotide probe in a predetermined location on the array. Each predetermined location may contain more than one molecule of the probe, but each molecule within the predetermined location has an identical sequence. Such predetermined locations are termed features. There may be, for example, from 2, 10, 100, 1000 to 10,000, 100,000 or 400,000 or more of such features on a single solid support. The solid support, or the area within which the probes are attached may be on the order of about a square centimeter. Probes corresponding to the genes of Tables 1-2 or from the related applications described above may be attached to single or multiple solid support structures, *e.g.*, the probes may be attached to a single chip or to multiple chips to comprise a chip set.

[0067] Oligonucleotide probe arrays, including bead assays or collections of beads, for expression monitoring can be made and used according to any techniques known in the art (see for example, Lockhart *et al.* (1996), *Nat Biotechnol* 14:1675-1680; McGall *et al.* (1996), *Proc Nat Acad Sci* USA 93: 13555-13460). Such probe arrays may contain at least two or more oligonucleotides that are complementary to or hybridize to two or more of the genes described in Table 2. For instance, such arrays may contain oligonucleotides that are complementary to or hybridize to at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 50, 70, 100, 500 or 1,000 or more of the genes described herein.

[0068] The sequences of the toxicity expression marker genes of Table 2 are in the public databases. Table 1 provides the SEQ ID NO: and GenBank Accession Number (NCBI RefSeq ID) for each of the sequences (see *www.ncbi.nlm.nih.gov/*), as well as the title for the cluster of which gene is part. The sequences of the genes in GenBank are expressly herein incorporated by reference in their entirety as of the filing date of this application, as are related sequences, for instance, sequences from the same gene of different lengths, variant sequences, polymorphic sequences, genomic sequences of the genes and related sequences from different species, including the human counterparts, where appropriate.

[0069] The terms "background" or "background signal intensity" refer to hybridization signals resulting from non-specific binding, or other interactions, between the labeled target nucleic acids and components of the oligonucleotide array (*e.g.*, the oligonucleotide probes, control probes, the array substrate, *etc.*). Background signals may also be produced by intrinsic fluorescence of the array components themselves. A single background signal can be calculated for the entire array, or a different background signal may be calculated for each target nucleic acid. In a preferred embodiment, background is calculated as the average hybridization signal intensity for the lowest 5% to 10% of the probes in the array, or, where a different background signal is calculated for each target gene, for the lowest 5% to 10% of the probes for each gene. Of course, one of skill in the art will appreciate that where the probes to a particular gene hybridize well and thus appear to be specifically binding to a target sequence, they should not be used in a background signal calculation. Alternatively, background may be calculated as the average hybridization signal intensity produced by hybridization to probes that are not complementary to any sequence found in the sample (*e.g.* probes directed to nucleic acids of the opposite sense or to genes not found in the sample such as bacterial genes where the sample is mammalian nucleic acids). Background can also be calculated as the average signal intensity produced by regions of the array that lack any probes at all.

[0070] The phrase "hybridizing specifically to" or "specifically hybridizes" refers to the binding, duplexing, or hybridizing of a molecule substantially to or only to a particular nucleotide sequence or sequences under stringent conditions when that sequence is present in a complex mixture (*e.g.*, total cellular) DNA or RNA.

[0071] As used herein a "probe" is defined as a nucleic acid, capable of binding to a target nucleic acid of complementary sequence through one or more types of chemical bonds, usually through complementary base pairing, usually through hydrogen bond formation. As used herein, a probe may include natural (*i.e.*, A, G, U, C, or T) or modified bases (7-deazaguanosine, inosine, *etc.*). In addition, the bases in probes may be joined by a linkage other than a phosphodiester bond, so long as it does not interfere with hybridization. Thus, probes may be peptide nucleic acids in which the constituent bases are joined by peptide bonds rather than phosphodiester linkages.

Nucleic Acid Samples

[0072] Cell or tissue samples may be exposed to the test agent *in vitro* or *in vivo*. When cultured cells or tissues are used, appropriate mammalian cell extracts, such as liver extracts, may also be added with the test agent to evaluate agents that may require biotransformation to exhibit toxicity. In a preferred format, primary isolates or cultured cell lines of animal or human renal cells may be used.

[0073] The genes which are assayed according to the present invention are typically in the form of mRNA or reverse transcribed mRNA. The genes may or may not be cloned. The genes may or may not be amplified. The cloning and/or amplification do not appear to bias the representation of genes within a population. In some assays, it may be preferable, however, to use polyA+ RNA as a source, as it can be used with fewer processing steps.

[0074] As is apparent to one of ordinary skill in the art, nucleic acid samples used in the methods and assays of the invention may be prepared by any available method or process. Methods of isolating total mRNA are well known to those of skill in the art. For example, methods of isolation and purification of nucleic acids are described in detail in Chapter 3 of Laboratory Techniques in Biochemistry and Molecular Biology, Vol. 24, Hybridization With Nucleic Acid Probes: Theory and Nucleic Acid Probes, P. Tijssen, Ed., Elsevier Press, New York, 1993. Such samples include RNA samples, but also include cDNA synthesized from a mRNA sample isolated from a cell or tissue of interest. Such samples also include DNA amplified from the cDNA, and RNA transcribed from the amplified DNA. One of skill in the art would appreciate that it is desirable to inhibit or destroy RNase present in homogenates before homogenates are used.

[0075] Biological samples may be of any biological tissue or fluid or cells from any organism as well as cells raised *in vitro*, such as cell lines and tissue culture cells. Frequently the sample will be a tissue or cell sample that has been exposed to a compound, agent, drug, pharmaceutical composition, potential environmental pollutant or other composition. In some formats, the sample will be a "clinical sample" which is a sample derived from a patient. Typical clinical samples include, but are not limited to, sputum, blood, blood-cells (*e.g.*, white cells), tissue or fine needle biopsy samples, urine, peritoneal fluid, and pleural fluid, or cells therefrom. Biological samples may also include sections of tissues, such as frozen sections or formalin fixed sections taken for histological purposes.

Hybridization

[0076] Nucleic acid hybridization simply involves contacting a probe and target nucleic acid under conditions where the probe and its complementary target can form stable hybrid duplexes through complementary base pairing. See WO 99/32660. The nucleic acids that do not form hybrid duplexes are then washed away leaving the hybridized nucleic acids to be detected, typically through detection of an attached detectable label. It is generally recognized that nucleic acids are denatured by increasing the temperature or decreasing the salt concentration of the buffer containing the nucleic acids. Under low stringency conditions (*e.g.*, low temperature and/or high salt) hybrid duplexes (*e.g.*, DNA:DNA, RNA:RNA, or RNA:DNA) will form even where the annealed sequences are not perfectly complementary. Thus, specificity of hybridization is reduced at lower stringency. Conversely, at higher stringency (*e.g.*, higher temperature or lower salt) successful hybridization tolerates fewer mismatches. One of skill in the art will appreciate that hybridization conditions may be selected to provide any degree of stringency.

[0077] In a preferred embodiment, hybridization is performed at low stringency, in this case in 6x SSPET at 37°C (0.005% Triton X-100), to ensure hybridization and then subsequent washes are performed at higher stringency (*e.g.*, 1x SSPET at 37°C) to eliminate mismatched hybrid duplexes. Successive washes may be performed at increasingly higher stringency (*e.g.*, down to as low as 0.25x SSPET at 37°C to 50°C) until a desired level of hybridization specificity is obtained. Stringency can also be increased by addition of agents such as formamide. Hybridization specificity may be evaluated by comparison of hybridization to the test probes with hybridization to the various controls that can be present (*e.g.*, expression level control, normalization control, mismatch controls, *etc.*).

[0078] In general, there is a tradeoff between hybridization specificity (stringency) and signal intensity. Thus, in a preferred embodiment, the wash is performed at the highest stringency that produces consistent results and that provides a signal intensity greater than the background intensity. Thus, in a preferred embodiment, the hybridized array may be washed at successively higher stringency solutions and read between each wash. Analysis of the data sets thus produced will reveal a wash stringency above which the hybridization pattern is not appreciably altered and which provides adequate signal for the particular oligonucleotide probes of interest.

Kits

[0079] The invention further includes kits combining, in different combinations, high-density oligonucleotide arrays, reagents for use with the arrays, signal detection and array-processing instruments, toxicology databases and analysis and database management software described above. The kits may be used, for example, to predict or model the toxic response of a test compound.

[0080] The databases that may be packaged with the kits are described above. In particular, the database software and packaged information may contain the databases saved to a computer-readable medium, or transferred to a user's local server. In another format, database and software information may be provided in a remote electronic format, such as a website, the address of which may be packaged in the kit.

[0081] Databases and software designed for use with microarrays are discussed in Balaban *et al.*, U.S. Patent Nos. 6,229,911, a computer-implemented method for managing information collected from small or large numbers of microarrays, and 6,185,561, a computer-based method with data mining capability for collecting gene expression level data, adding additional attributes and reformatting the data to produce answers to various queries. Chee *et al.*, U.S. Patent No. 5,974,164, disclose a software-based method for identifying mutations in a nucleic acid sequence based on differences in probe fluorescence intensities between wild type and mutant sequences that hybridize to reference sequences.

[0082] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. The following working examples therefore, specifically point out the preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

EXAMPLES

Example 1: Generation of Toxicity Models using RMA and PLS

[0083] Various kidney toxins are administered to male Sprague-Dawley rats at various timepoints using administration diluents, protocols and dosing regimes as previously described in the art and previously described in the priority application discussed above. .

As an illustration of the protocols used, the toxins are administered to and animals are sacrificed and kidney samples harvested at the time points indicated below.

OBSERVATION OF ANIMALS

[0084] 1. Clinical cage side observations- twice daily mortality and moribundity check. Skin and fur, eyes and mucous membrane, respiratory system, circulatory system, autonomic and central nervous system, somatomotor pattern, and behavior pattern are checked. Potential signs of toxicity, including tremors, convulsions, salivation, diarrhea, lethargy, coma or other atypical behavior or appearance, are recorded as they occur and include a time of onset, degree, and duration.

[0085] 2. Physical Examinations-Prior to randomization, prior to initial treatment, and prior to sacrifice.

[0086] 3. Body Weights-Prior to randomization, prior to initial treatment, and prior to sacrifice.

CLINICAL PATHOLOGY

[0087] 1. Frequency- Prior to necropsy.

[0088] 2. Number of animals-All surviving animals.

[0089] 3. Bleeding Procedure-Blood was obtained by puncture of the orbital sinus while under 70% CO_2/ 30% O_2 anesthesia.

[0090] 4. Collection of Blood Samples-Approximately 0.5 mL of blood is collected into EDTA tubes for evaluation of hematology parameters. Approximately 1 mL of blood is collected into serum separator tubes for clinical chemistry analysis. Approximately 200 µL of plasma is obtained and frozen at ~-80°C for test compound/metabolite estimation. An additional ~2 mL of blood is collected into a 15 mL conical polypropylene vial to which ~3 mL of Trizol is immediately added. The contents are immediately mixed with a vortex and by repeated inversion. The tubes are frozen in liquid nitrogen and stored at —80°C.

TERMINATION PROCEDURES

Terminal Sacrifice

[0091] At the time points indicated above, rats are weighed, physically examined, sacrificed by decapitation, and exsanguinated. The animals are necropsied within approximately five

minutes of sacrifice. Separate sterile, disposable instruments are used for each animal. Necropsies are conducted on each animal following procedures approved by board-certified pathologists.

[0092] Animals not surviving until terminal sacrifice are discarded without necropsy (following euthanasia by carbon dioxide asphyxiation, if moribund). The approximate time of death for moribund or found dead animals is recorded.

Postmortem Procedures

[0093] All tissues are collected and frozen within approximately 5 minutes of the animal's death. Tissues are stored at approximately -80°C or preserved in 10% neutral buffered formalin.

Tissue Collection and Processing

[0094] Liver

1. Right medial lobe -snap freeze in liquid nitrogen and store at ~-80°C.
2. Left medial lobe -Preserve in 10% neutral-buffered formalin (NBF) and evaluate for gross and microscopic pathology.
3. Left lateral lobe -snap freeze in liquid nitrogen and store at ~-80°C.

[0095] Heart

1. A sagittal cross-section containing portions of the two atria and of the two ventricles is preserved in 10% NBF. The remaining heart is frozen in liquid nitrogen and stored at ~ -80°C.

[0096] Kidneys (both)

1. Left – Hemi-dissect; half is preserved in 10% NBF and the remaining half is frozen in liquid nitrogen and stored at ~ -80°C.
2. Right – Hemi-dissect; half is preserved in 10% NBF and the remaining half is frozen in liquid nitrogen and stored at ~ -80°C.

[0097] Testes (both)-A sagittal cross-section of each testis is preserved in 10% NBF. The remaining testes are frozen together in liquid nitrogen and stored at ~-80°C.

[0098] Brain (whole)-A cross-section of the cerebral hemispheres and of the diencephalon are preserved in 10% NBF, and the rest of the brain is frozen in liquid nitrogen and stored at ~ -80°C.

[0099] Microarray sample preparation is conducted with minor modifications, following the protocols set forth in the Affymetrix GeneChip® Expression Technical Analysis Manual (Affymetrix, Inc. Santa Clara, CA). Frozen tissue is ground to a powder using a Spex Certiprep 6800 Freezer Mill. Total RNA is extracted with Trizol (Invitrogen, Carlsbad CA) utilizing the manufacturer's protocol. mRNA is isolated using the Oligotex mRNA Midi kit (Qiagen) followed by ethanol precipitation. Double stranded cDNA is generated from mRNA using the SuperScript Choice system (Invitrogen, Carlsbad CA). First strand cDNA synthesis is primed with a T7-(dT24) oligonucleotide. The cDNA is phenol-chloroform extracted and ethanol precipitated to a final concentration of 1 μg/ml. From 2 μg of cDNA, cRNA is synthesized using Ambion's T7 MegaScript in vitro Transcription Kit.

[00100] To biotin label the cRNA, nucleotides Bio-11-CTP and Bio-16-UTP (Enzo Diagnostics) are added to the reaction. Following a 37°C incubation for six hours, impurities are removed from the labeled cRNA following the RNeasy Mini kit protocol (Qiagen). cRNA is fragmented (fragmentation buffer consisting of 200 mM Tris-acetate, pH 8.1, 500 mM KOAc, 150 mM MgOAc) for thirty-five minutes at 94°C. Following the Affymetrix protocol, 55 μg of fragmented cRNA is hybridized on the Affymetrix rat array set for twenty-four hours at 60 rpm in a 45°C hybridization oven. The chips are washed and stained with Streptavidin Phycoerythrin (SAPE) (Molecular Probes) in Affymetrix fluidics stations. To amplify staining, SAPE solution is added twice with an anti-streptavidin biotinylated antibody (Vector Laboratories) staining step in between. Hybridization to the probe arrays is detected by fluorometric scanning (Hewlett Packard Gene Array Scanner). Data is analyzed using Affymetrix GeneChip® and Expression Data Mining (EDMT) software, the GeneExpress® database, and S-Plus® statistical analysis software (Insightful Corp.).

Identification of Toxicity Markers and Model Building using RMA and PLS Algorithms

[00101] RMA/PLS models are built as follows. From DNA microarray data from one or more studies, a matrix of RMA fold-change expression values is generated. These values are generated, for example, according to the method of Irizarry *et al.* (*Nucl Acids Res* 31(4):e15, 2003), which uses the following equation to produce a log scale linear additive model: $T(PM_{ij}) = e_i + a_j + \varepsilon_{ij}$. T represents the transformation that corrects for background and normalizes and converts the PM (perfect match) intensities to a log scale. e_i represents the log2 scale expression values found on arrays $i = 1 - I$, a_j represents the log scale affinity

effects for probes j = 1 – J, and ε_{ij} represents error (to correct for the differences in variances when using probes that bind with different intensities).

[00102] In RMA fold-change matrices, the rows represent individual fragments, and the columns are individual samples. A vehicle cohort median matrix is then calculated, in which the rows represent fragments and the columns represent vehicle cohorts, one cohort for each study/time-point combination. The values in this matrix are the median RMA expression values across the samples within those cohorts. Next, a matrix of normalized RMA expression values is generated, in which the rows represent individual fragments and the columns are individual samples. The normalized RMA values are the RMA values minus the value from the vehicle cohort median matrix corresponding to the time-matched vehicle cohort. PLS modeling is then applied to the normalized RMA matrix (a subset by taking certain fragments as described below), using a –1 = non-tox, +1 = tox supervised score vector as the dependant variable and the rows of normalized RMA matrix as the independent variables. PLS works by computing a series of PLS components, where each component is a weighted linear combination of fragment values. We use the nonlinear iterative partial least squares method to compute the PLS components.

[00103] To select fragments, a vehicle cohort mean matrix is generated, in which the rows represent fragments and the columns represent vehicle cohorts, one cohort for each study/time-point combination. The values in this matrix are the mean RMA expression values across the samples within those cohorts. A treated cohort mean matrix is then generated, in which the rows represent fragments and the columns represent treated (non-vehicle) cohorts, one cohort for each study/time-point/compound/dose combination. The values in this matrix are the mean RMA expression values across the samples within those cohorts. Next, a treated cohort fold-change matrix is generated, in which the rows represent fragments and the columns represent treated cohorts, one cohort for each study/time-point/compound/dose combination. The values in this matrix are the values in the treated cohort mean matrix minus the values in the vehicle cohort mean matrix corresponding to appropriate time-matched vehicle cohorts. Subsequently, a treated cohort p-value matrix is generated, in which the rows represent fragments and the columns represent treated cohorts, one cohort for each study/time-point/compound/dose combination. The values in this matrix are p-values based on two-sample t-tests comparing the treated cohort mean values to the vehicle cohort mean values corresponding to appropriate time-matched vehicle cohorts. This

matrix is converted to a binary coding based on the p-values being less than 0.05 (coded as 1) or greater than 0.05 (coded as 0).

[00104] The row sums of the binary treated cohort p-value matrix are computed, where that row sum represents a "gene regulation score" for each fragment, representing the total number of treated cohorts where the fragment showed differential regulation (up- or down-regulation) compared to its time-matched vehicle cohort. PLS modeling and 2/3 / 1/3 cross-validation are then performed based on taking the top N fragments according to the regulation score, varying N and the number of PLS components, and recording the model success rate for each combination. N is chosen to be the point at which the cross-validated error rate are minimized. In the PLS model, each of those N fragments receives a PLS weight (PLS score) corresponding to the fragment's utility, or predictive ability, in the model (see Table 2 for an exemplary list of PLS scores for a kidney general toxicity model).

Example 2: Methods of predicting at least one toxic effect of a test agent

[00105] To determine whether or not a sample from an animal treated with a test agent or compound exhibits at least one toxic effect or response, RNA is prepared from a cell or tissue sample exposed to the agent and hybridized to a DNA microarray, as described in Example 1 above. From the nucleic acid hybridization data, a prediction score is calculated for that sample and compared to a reference score from a toxicity reference database according to the following equation. The sample prediction score = $\Sigma\, w_i\, R^{FC_i}$. "i" is the index number for each gene in a gene expression profile to be evaluated. "w_i" is the PLS weight (or PLS score, see Table 2 for an exemplary list of PLS scores for a general kidney toxicity model) for each gene. "R^{FC_i}" is the RMA fold-change value for the i^{th} gene, as determined from a normalized RMA matrix of gene expression data from the sample (described above). The PLS weight multiplied by the RMA fold-change value gives a gene regulation score for each gene, and the regulation scores for all the individual genes are added to give a prediction score for the sample.

[00106] As a quality control (QC) check, for each incoming study, an average correlation assessment is performed. After the RMA matrix is generated (genes by samples), a Pearson correlation matrix is calculated of the samples to each other. This matrix is samples by samples. For each sample row of the matrix, the mean of all correlation values in that row of the matrix, excluding the diagonal (which is always 1) is calculated. This mean is the

average correlation for that sample. If the average correlation is less than a threshold (for instance .90), the sample is flagged as a potential outlier. This process is repeated for each row (sample) in the study. Outliers flagged by the average correlation QC check are dropped out of any downstream normalization, prediction or compound similarity steps in the process.

[00107] To establish a toxicity prediction score cut-off value for a toxicity model, the true-positive and false positive rates for each possible score cut-off value are computed, using the scores from all tox and non-tox samples in the training set. This generates an ROC curve, which we use to set the cut-off score at the point on the ROC curve corresponding to ~5% false positive rate. For example, in a kidney toxicity model of Table 2, a cut-off prediction score is about 0.318. If the sample score is about 0.318 or above, it can be predicted that the sample shows a toxic response after exposure to the test compound. If the sample score is below 0.318, it can be predicted that the sample does not show a toxic response

[00108] The model can be trained by setting a score of −1 for each gene that cannot predict a toxic response and by setting a score of +1 for each gene that can predict a toxic response. Cross-validation of RMA/PLS models may be performed by the compound-drop method and by the 2/3:1/3 method. In the compound-drop method, sample data from animals treated with one particular test compound are removed from a model, and the ability of this model to predict toxicity is compared to that of a model containing a full data set. In the 2/3:1/3 method, gene expression information from a random third of the genes in the model is removed, and the ability of this subset model to predict toxicity is compared to that of a model containing a full data set.

[00109] Compound similarity is assessed in the following way. In the same manner as described above, a cohort fold-change vector for each study/time-point/compound/dose combination is calculated. This vector is reduced to only the fragments used in the PLS predictive models. We then calculate Pearson correlations for that cohort fold-change vector with each cohort vector (also reduced to only the fragments used in the PLS predictive models) in our reference database. Finally, these Pearson correlations are ranked from highest to lowest and the results are reported.

[00110] A report may be generated comprising information or data related to the results of the methods of predicting at least one toxic effect. The report may comprise information related to the toxic effects predicted by the comparison of at least one sample prediction score to at least one toxicity reference prediction score from the database. The report may also

present information concerning the nucleic acid hybridization data, such as the integrity of the data as well as information inputted by the user of the database and methods of the invention, such as information used to annotate the nucleic acid hybridization data. See PCT US02/22701 for a non-limiting example of a toxicity report that may be generated.

Example 3: Converting RMA data from one platform to another

[00111] An algorithm was developed to convert probe intensity data from a first type of microarray to RMA data of a second type of microarray. This is beneficial to the customer because it provides the customer with the freedom to select the type of microarray it wishes to use with a RMA/PLS predictive model. Frequently this is the newest microarray on the market. The algorithm is beneficial for the company which builds RMA/PLS statistical models on microarray data because money and resources do not have to be expended to rebuild statistical models built on discontinued microarrays.

[00112] The conversion algorithm developed can be used on data from the Affymetrix GeneChip® rat RAE 2.0 microarray to Affymetrix GeneChip® rat RGU34 A microarray data. This conversion also allows the use of RMA/PLS toxicogenomics models built on the Affymetrix RGU34 A microarray platform to predict customer data generated on the RAE2.0 microarray platform. The conversion algorithm was tested using the liver toxicity model described in U.S. Provisional Application Serial No. 60/559,949 and herein incorporated by reference.

[00113] The first step to using a conversion algorithm is to map microarray fragments. The RGU34 A microarray fragments which comprise the liver toxicity model were mapped to the RAE2.0 microarray. The liver toxicity model is based on 1,100 Affymetrix GeneChip® RGU34 A microarray fragments. Of the 1,100 fragments in the model, 907 were suggested by Affymetrix as matching to fragments on the RAE2.0 microarray. See Affymetrix's "User's Guide to Product Comparison Spreadsheets" which is herein incorporated by reference. Another 105 fragments mapped to fragments sharing the same RefSeq ID and 55 mapped to fragments which mapped to the same UniGene cluster. The 1067 mapping fragments were reduced to 1053. The 1053 mapped fragments represented 16 RGU34 A and 11 RAE 2.0 probes. The 47 fragments which were not mapped to the RAE2.0 microarray

were assigned an RMA fold-change value of 0 for all samples and did not contribute to the prediction.

[00114] Once the microarray fragments are mapped, training samples are selected to calculate the conversion model weights. The inventors searched Gene Logic's ToxExpress® reference database, a database which is built on the Affymetrix RGU34A platform, for samples that covered a large amount of interquartile range with respect to signal intensity. Samples that covered the largest amount of variable space were selected because this method of sample selection had previously been determined by the inventors to be reliable in the development of a human sample conversion algorithm. The samples maximized Σ_i ($Max(X_{ij})$ – $Min(X_{ij})$), where i indexes genes and j indexes samples.

[00115] The inventors found that sample size calculations were stable at a sampling of approximately 100 microarrays. For this reason, a training set consisting of 100 compounds and vehicles from rat liver tissue was selected.

[00116] The 100 training samples were used to train the weights in the conversion algorithm. This step is important because it provides for the quantitative aspect of the conversion. The weight training was performed based on a multiple regression analysis with probe values as the independent variables and RMA expression as the sum of the dependent variables.

[00117] Test samples were evaluated using the trained conversion algorithm. The multiple regression model was built on the 11 perfect match probe intensities and generated a predicted RGU34 expression value from a weighted sum of RAE 2.0 probe values. Each test array was scaled to an average probe intensity of 10 (log scale). The conversion algorithm used is given as:

$$Y_i^{RGU34} = \beta_{iO} + \Sigma\beta i_J \, LOG \, (Xi_J^{RAE2.0}/S)$$

where Y is the RGU34 RMA expression value for a fragment; $X_{ij}^{RAE2.0}$ for i=1...1053, j=1...11 are perfect match probe intensity values for the marker genes on the RAE2.0 microarray; S is a chip scale factor $\Sigma_{ij} X_{ij}^{RAE2.0}/n$. Probe intensities were first floored to the minimum intensity value of 30.

[00118] Alternative approaches to using a multiple regression model exist to convert RAE2.0 data to RGU34 RMA data. Non-linear regression on probe values as well as canonical correlation of RAE2.0 probes to RGU34 A probes could be used. RMA values on

a RAE2.0 microarray could be computed and then scaled or quantile-normalized to RGU34 A RMA values. In addition, although the multiple regression analysis used in this example does not take into account mismatched probes, an analysis could be used which takes into account mismatched probes.

[00119] The liver predictive model was used to compare the predictive results of test data from the RGU34 microarray to test data derived from converted RAE2.0 array data. The consistency between the RGU34 array results and the converted RAE2.0 array results was quite high. Table 3 provides the number of test samples per compound which were predicted as toxic out of the total number of samples for that compound using RGU34 RMA data and RAE2.0 converted RMA data. Amitryptilene, estradiol, amiodarone, diflunisal, phenobarbital, dioxin, ethionine, and LPS were selected as test toxicants. Clofibrate was selected because it is a rat-specific toxicant. Metformin, rosiglitazone, chlorpheniramine, and streptomycin were selected as test negative controls. The rat-specific toxicant and all of the tested negative controls correctly predicted no toxicity.

Table 3

Treatment	*RGU34*	*RAE2.0 converted*
Amitryptilene	1/2	2/2
Estradiol	3/3	3/3
Amiodarone	2/3	2/3
Diflunisal	2/3	2/3
Phenobarbital	3/3	3/3
Dioxin	3/3	2/3
Ethionine	3/3	3/3
LPS	3/3	3/3
Clofibrate	0/3	0/3
Metformin	0/3	0/3
Rosiglitazone	0/3	0/3
Chlorpheniramine	0/3	0/3
Streptomycin	0/3	0/3

Example 4: Database

[00120] A web-based software predictive modeling system called the ToxShield™ Suite was created which is composed of a collection of RMA/PLS toxicity predictive models. Liver RMA/PLS predictive models were built to allow a user to identify and classify various toxic and mechanistic responses to unknown or test compounds. The models represent a wide variety of endpoint pathologies and indications, including general toxicity, necrosis, steatosis, macrovesicular steatosis, microvesicular steatosis, cholestasis, hepatitis, carcinogenicity, genotoxic carcinogenicity, non-genotoxic carcinogenicity, rat specific non-genotoxic carcinogenicity, peroxisome proliferation, and inducer/liver enlargement. The outcome of toxicity models represents a detailed categorization of test or unknown compounds from which mechanistic information can be inferred. Although the current models available as part of this software system are related to liver toxicity, models relating to specific toxicities of other organs including, but not limited to, liver primary cell culture, kidney, heart, spleen, bone marrow, and brain could be used.

[00121] The conversion algorithm described in Example 3 can be implemented in a software product such as the ToxShield™ Suite. The customer inputs his or her data that has been generated on a microarray such as the Affymetrix RAE2.0 GeneChip® microarray platform. The software utilizes the algorithm to convert the customer's gene expression data to RMA data which is compatible with the software's toxicogenomics model built which was built exclusively on a second microarray platform such as the Affymetrix RGU34 A GeneChip® microarray. Visualizations and predictions can then be generated from the customer's data using the predictive model.

[00122] Although the present invention has been described in detail with reference to examples above, it is understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims. All cited patents, patent applications and publications referred to in this application are herein incorporated by reference in their entirety.

Table1 Atty Ref: 44921-5133.WO

GLGC Identifier	Seq ID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
25098	2	AA108277		
18396	8	AA799330		Rattus norvegicus transcribed sequence with strong similarity to protein ref:NP_057030.1 (H.sapiens) CGI-17 protein; pelota (Drosophila) homolog [Homo sapiens]
18291	12	AA799497		Rattus norvegicus transcribed sequences
23063	14	AA799534		Rattus norvegicus transcribed sequences
18361	16	AA799591		Rattus norvegicus transcribed sequence with strong similarity to protein prf:1202265A (R.norvegicus) 1202265A tubulin T beta15 [Rattus norvegicus]
14309	19	AA799676		Rattus norvegicus transcribed sequences
21007	22	AA799861		Rattus norvegicus transcribed sequence with strong similarity to protein sp.P70434 (M.musculus) IRF7_MOUSE Interferon regulatory factor 7 (IRF-7)
23203	23	AA799971		Rattus norvegicus transcribed sequence with moderate similarity to protein ref:NP_060761.1 (H.sapiens) hypothetical protein FLJ10986 [Homo sapiens]
4412	26	AA800005	CD151 antigen	CD151 antigen
21035	27	AA800025		Rattus norvegicus transcribed sequence with strong similarity to protein ref:NP_542787.1 (H.sapiens) chromosome 20 open reading frame 163 [Homo sapiens]
18462	32	AA800708		Rattus norvegicus transcribed sequences
22386	37	AA800844		Rattus norvegicus transcribed sequence with moderate similarity to protein sp:P16636 (R.norvegicus) LYOX_RAT Protein-lysine 6-oxidase precursor (Lysyl oxidase)
15022	38	AA801029	nuclear receptor subfamily 2, group F, member 6	nuclear receptor subfamily 2, group F, member 6
20753	43	AA801441	platelet-activating factor acetylhydrolase beta subunit (PAF-AH beta)	platelet-activating factor acetylhydrolase beta subunit (PAF-AH beta)
2109	47	AA817887	profilin	profilin
9125	67	AA819338	signal sequence receptor 4	signal sequence receptor 4
8888	81	AA849036	guanylate cyclase 1, soluble, alpha 3	guanylate cyclase 1, soluble, alpha 3
1867	91	AA850940	ribosomal protein L4	ribosomal protein L4
17411	102	AA858621	CaM-kinase II inhibitor alpha	CaM-kinase II inhibitor alpha
12700	104	AA858673	pancreatic secretory trypsin inhibitor type II (PSTI-II)	pancreatic secretory trypsin inhibitor type II (PSTI-II)
14124	112	AA859305	tropomyosin isoform 6	tropomyosin isoform 6

Table 1 Atty. Ref. 44921-5133.WO

GLGC Identifier	Seq ID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
4178	114	AA859536		Rattus norvegicus transcribed sequence with strong similarity to protein sp:P07153 (R.norvegicus) RIB1_RAT Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 67 kDa subunit precursor (Ribophorin I) (RPN-I)
15150	115	AA859562		
11852	117	AA859593		Rattus norvegicus transcribed sequence with moderate similarity to protein pdb:1LBG (E. coli) B Chain B, Lactose Operon Repressor Bound To 21-Base Pair Symmetric Operator Dna, Alpha Carbons Only
4809	118	AA859616		Rattus norvegicus transcribed sequence with weak similarity to protein ref:NP_502422.1 (C.elegans) FYVE zinc finger [Caenorhabditis elegans]
19067	119	AA859663		Rattus norvegicus transcribed sequence with weak similarity to protein ref:NP_080153.1 (M.musculus) RIKEN cDNA 2310067G05 [Mus musculus]
20582	120	AA859688		Rattus norvegicus transcribed sequence with weak similarity to protein pdb:1DUB (R.norvegicus) F Chain F, 2-Enoyl-Coa Hydratase, Data Collected At 100 K, Ph 6.5
22374	122	AA859804		Rattus norvegicus transcribed sequence with weak similarity to protein sp:P20415 (R.norvegicus) IF4E_MOUSE EUKARYOTIC TRANSLATION INITIATION FACTOR 4E (EIF-4E) (EIF4E) (MRNA CAP-BINDING PROTEIN) (EIF-4F 25 KDA SUBUNIT)
22927	127	AA859920	nucleosome assembly protein 1-like 1	nucleosome assembly protein 1-like 1
4222	132	AA860024		Rattus norvegicus transcribed sequence with strong similarity to protein sp:Q9D8N0 (M.musculus) EF1G_MOUSE Elongation factor 1-gamma (EF-1-gamma) (eEF-1B gamma)
7090	134	AA860039		Rattus norvegicus transcribed sequence
15927	137	AA866321		Rattus norvegicus transcribed sequences
11865	138	AA866383		Rattus norvegicus transcribed sequences
19402	140	AA874848	Thymus cell surface antigen	Thymus cell surface antigen
16139	146	AA874927		Rattus norvegicus transcribed sequences
6451	148	AA875033	fibulin 5	fibulin 5
16419	149	AA875102		Rattus norvegicus transcribed sequence with strong similarity to protein sp:P08578 (M.musculus) RUXE_HUMAN Small nuclear ribonucleoprotein E (snRNP-E) (Sm protein E) (Sm-E) (SmE)

Table 1				Atty Ref: 44921-5133-WO
GLGC Identifier	Seq ID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
18084	151	AA875186		
15371	152	AA875205		Rattus norvegicus transcribed sequence with strong similarity to protein sp:P55884 (H.sapiens) IF39_HUMAN Eukaryotic translation initiation factor 3 subunit 9 (eIF-3 eta) (eIF3 p116) (eIF3 p110)
15376	153	AA875206	ubiquilin 1	ubiquilin 1
15887	154	AA875225	GTP-binding protein (G-alpha-i2)	GTP-binding protein (G-alpha-i2)
15888	154	AA875225	GTP-binding protein (G-alpha-i2)	GTP-binding protein (G-alpha-i2)
15401	155	AA875257		Rattus norvegicus transcribed sequences
18902	158	AA875390	thioredoxin-like (32kD)	thioredoxin-like (32kD)
15505	159	AA875414		Rattus norvegicus transcribed sequence with weak similarity to protein ref:NP_059088.1 (M.musculus) cadherin EGF LAG seven-pass G-type receptor 2 [Mus musculus]
6153	162	AA875531		
24235	169	AA891286	thioredoxin reductase 1	thioredoxin reductase 1
9952	170	AA891422	hypoxia induced gene 1	hypoxia induced gene 1
9071	172	AA891578		Rattus norvegicus transcribed sequences
474	173	AA891670		Rattus norvegicus transcribed sequence with moderate similarity to protein ref:NP_034894.1 (M.musculus) mannosidase 2, alpha B1; lysosomal alpha-mannosidase [Mus musculus]
9091	174	AA891690		Rattus norvegicus transcribed sequence with strong similarity to protein ref:NP_076006.1 (M.musculus) tumor necrosis factor (ligand) superfamily, member 13 [Mus musculus]
17420	175	AA891693		Rattus norvegicus transcribed sequences
18078	176	AA891726	solute carrier family 34, member 1	solute carrier family 34, member 1
20839	177	AA891729	ribosomal protein S27a	ribosomal protein S27a
11959	178	AA891735		Rattus norvegicus transcribed sequences
17693	179	AA891737		Rattus norvegicus transcribed sequences
17289	185	AA891785		Rattus norvegicus transcribed sequence with weak similarity to protein sp:P41562 (R.norvegicus) IDHC_RAT ISOCITRATE DEHYDROGENASE [NADP] CYTOPLASMIC (OXALOSUCCINATE DECARBOXYLASE) (IDH) (NADP+-SPECIFIC ICDH) (IDP)

Table 1 Atty Ref: 44921-5133-WO

GLGC Identifier	Seq ID	GenBank Accor RefSeq ID	Known Gene Name	UniGene Cluster Title
17290	185	AA891785		Rattus norvegicus transcribed sequence with weak similarity to protein sp:P41562 (R.norvegicus) IDHC_RAT ISOCITRATE DEHYDROGENASE [NADP] CYTOPLASMIC (OXALOSUCCINATE DECARBOXYLASE) (IDH) (NADP+-SPECIFIC ICDH) (IDP)
20522	190	AA891842		Rattus norvegicus transcribed sequence with weak similarity to protein ref:NP_057713.1 (H.sapiens) hypothetical protein LOC51323 [Homo sapiens]
20523	190	AA891842		Rattus norvegicus transcribed sequence with weak similarity to protein ref:NP_057713.1 (H.sapiens) hypothetical protein LOC51323 [Homo sapiens]
17249	191	AA891858		Rattus norvegicus transcribed sequence with moderate similarity to protein sp:O88338 (M.musculus) CADG_MOUSE Cadherin-16 precursor (Kidney-specific cadherin) (Ksp-cadherin)
16023	192	AA891872		Rattus norvegicus transcribed sequence with strong similarity to protein pir:S54876 (M.musculus) S54876 NAD(P)+ transhydrogenase (B-specific) (EC 1.6.1.1) precursor - mouse
17779	194	AA891914		Rattus norvegicus transcribed sequence with moderate similarity to protein pir:A47488 (H.sapiens) A47488 aminoacylase (EC 3.5.1.14) - human
1159	197	AA891949		Rattus norvegicus transcribed sequences
17630	201	AA892012	glutamate oxaloacetate transaminase 2	glutamate oxaloacetate transaminase 2
13420	205	AA892042		Rattus norvegicus transcribed sequence with weak similarity to protein pir:JC2534 (R.norvegicus) JC2534 RVLG protein - rat
4259	207	AA892123	ribosomal protein L36	ribosomal protein L36
14595	208	AA892128		Rattus norvegicus transcribed sequences
16529	210	AA892154		Rattus norvegicus transcribed sequence with moderate similarity to protein pdb:1LBG (E. coli) B Chain B, Lactose Operon Repressor Bound To 21-Base Pair Symmetric Operator Dna, Alpha Carbons Only
4482	211	AA892173		Rattus norvegicus transcribed sequence
8317	212	AA892234		Rattus norvegicus transcribed sequence with strong similarity to protein ref:NP_079845.1 (M.musculus) microsomal glutathione S-transferase 3 [Mus musculus]
4484	213	AA892258	NADPH oxidase 4	NADPH oxidase 4
18190	215	AA892280		Rattus norvegicus transcribed sequences

Table 1 Atty Ref: 4492175133-WO

GLGC Identifier	Seq ID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
17717	216	AA892287		Rattus norvegicus transcribed sequence with weak similarity to protein ref:NP_061123.2 (H.sapiens) G protein-coupled receptor, family C, group 5, member C, isoform b, precursor; orphan G-protein coupled receptor; retinoic acid inducible gene 3 protein; retinoic acid responsive gene protein [Homo sapiens]
9027	218	AA892312	potassium inwardly-rectifying channel, subfamily J, member 16	potassium inwardly-rectifying channel, subfamily J, member 16
13647	221	AA892367		Rattus norvegicus transcribed sequence with strong similarity to protein sp:P21531 (R.norvegicus) RL3_RAT 60S RIBOSOMAL PROTEIN L3 (L4)
820	225	AA892395	aldolase B	(Rattus norvegicus transcribed sequence with strong similarity to protein sp:P00884 (R.norvegicus) ALFB_RAT FRUCTOSE-BISPHOSPHATE ALDOLASE B (LIVER-TYPE ALDOLASE), aldolase B)
12016	226	AA892404	Na+ dependent glucose transporter 1	Na+ dependent glucose transporter 1
21695	231	AA892506	coronin, actin binding protein 1A	coronin, actin binding protein 1A
4499	232	AA892511		Rattus norvegicus transcribed sequence with weak similarity to protein ref:NP_077053.1 (R.norvegicus) calcium binding protein P22 [Rattus norvegicus]
8599	233	AA892522		Rattus norvegicus transcribed sequences
15154	234	AA892532	protein disulfide isomerase-related protein	protein disulfide isomerase-related protein
12276	235	AA892541		Rattus norvegicus transcribed sequences
12275	235	AA892541		Rattus norvegicus transcribed sequences
18275	239	AA892572		Rattus norvegicus transcribed sequence with strong similarity to protein ref:NP_079639.1 (M.musculus) RIKEN cDNA 1110001J03 [Mus musculus]
18274	239	AA892572		Rattus norvegicus transcribed sequence with strong similarity to protein ref:NP_079639.1 (M.musculus) RIKEN cDNA 1110001J03 [Mus musculus]
4512	240	AA892578		Rattus norvegicus transcribed sequence with strong similarity to protein ref:NP_116238.1 (H.sapiens) hypothetical protein FLJ14834 [Homo sapiens]
15876	241	AA892582	aldehyde dehydrogenase family 3, member A1	aldehyde dehydrogenase family 3, member A1
17500	243	AA892616	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3

Table 1				Atty Ref:44921-5133-WO
GLGC Identifier	Seq ID	GenBank Accor RefSeq ID	Known Gene Name	UniGene Cluster Title
23783	245	AA892773		Rattus norvegicus transcribed sequence with moderate similarity to protein pdb:1LBG (E. coli) B Chain B, Lactose Operon Repressor Bound To 21-Base Pair Symmetric Operator Dna, Alpha Carbons Only
13542	247	AA892798	uterine sensitization-associated gene 1 protein	uterine sensitization-associated gene 1 protein
22539	248	AA892799		Rattus norvegicus transcribed sequence with weak similarity to protein ref:NP_113808.1 (R.norvegicus) 3-phosphoglycerate dehydrogenase [Rattus norvegicus]
15385	249	AA892808	isocitrate dehydrogenase 3, gamma	isocitrate dehydrogenase 3, gamma
23322	252	AA892821	aldo-keto reductase family 7, member A2 (aflatoxin aldehyde reductase)	aldo-keto reductase family 7, member A2 (aflatoxin aldehyde reductase)
12848	257	AA892916		Rattus norvegicus Ab2-305 mRNA, complete cds
3853	260	AA892999		Rattus norvegicus transcribed sequences
3439	261	AA893000		Rattus norvegicus transcribed sequence with strong similarity to protein pir:T00335 (H.sapiens) T00335 hypothetical protein KIAA0564 - human (fragment)
12020	262	AA893035	HP33	HP33
3870	266	AA893147		Rattus norvegicus transcribed sequences
548	271	AA893235		Rattus norvegicus transcribed sequence with strong similarity to protein sp:Q61585 (M.musculus) G0S2_MOUSE Putative lymphocyte G0/G1 switch protein 2 (G0S2-like protein)
17752	272	AA893244		Rattus norvegicus transcribed sequences
18967	273	AA893260		Rattus norvegicus transcribed sequence with weak similarity to protein ref:NP_083358.1 (M.musculus) RIKEN cDNA 5830411J07 [Mus musculus]
4242	276	AA893325	ornithine aminotransferase	ornithine aminotransferase
7505	282	AA893702	transcobalamin II precursor	transcobalamin II precursor
9084	283	AA893717		Rattus norvegicus transcribed sequence with strong similarity to protein ref:NP_036155.1 (M.musculus) Rac GTPase-activating protein 1 [Mus musculus]
10540	286	AA894027		
3895	287	AA894029		Rattus norvegicus transcribed sequences

Table 1				Atty. Ref: 4492155133:WO
GLGC Identifier	Seq ID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
16435	290	AA894174		Rattus norvegicus transcribed sequence with strong similarity to protein pir:A31568 (R.norvegicus) A31568 electron transfer flavoprotein alpha chain precursor - rat
16849	292	AA894298	membrane metallo endopeptidase	membrane metallo endopeptidase
24329	294	AA899253	myristoylated alanine rich protein kinase C substrate	myristoylated alanine rich protein kinase C substrate
23778	298	AA899854	topoisomerase (DNA) 2 alpha	topoisomerase (DNA) 2 alpha
9541	300	AA900505	rhoB gene	rhoB gene
20711	307	AA924267	cytochrome P450,4A1	cytochrome P450,4A1
17157	329	AA926129		Rattus norvegicus transcribed sequence with strong similarity to protein ref:NP_446139.1 (R.norvegicus) schlafen 4 [Rattus norvegicus]
16468	330	AA926137		Rattus norvegicus transcribed sequence with strong similarity to protein ref:NP_079926.1 (M.musculus) RIKEN cDNA 0710008D09 [Mus musculus]
15028	336	AA942685	cytosolic cysteine dioxygenase 1	cytosolic cysteine dioxygenase 1
21696	346	AA944324	ADP-ribosylation factor 6	ADP-ribosylation factor 6
20812	356	AA945611	ribosomal protein L10	ribosomal protein L10
22351	361	AA945867	v-jun sarcoma virus 17 oncogene homolog (avian)	v-jun sarcoma virus 17 oncogene homolog (avian)
1509	435	AB000507	aquaporin 7	aquaporin 7
17337	436	AB000717		
7914	439	AB002584	beta-alanine-pyruvate aminotransferase	beta-alanine-pyruvate aminotransferase
15703	444	AB009372	lysophospholipase	lysophospholipase
15662	445	AB010119	t-complex testis expressed 1	t-complex testis expressed 1
4312	448	AB010635	carboxylesterase 2 (intestine, liver)	carboxylesterase 2 (intestine, liver)
13973	449	AB011679	tubulin, beta 5	tubulin, beta 5
18075	454	AB013455	solute carrier family 34, member 1	solute carrier family 34, member 1
18076	454	AB013455	solute carrier family 34, member 1	solute carrier family 34, member 1
18597	455	AB013732	UDP-glucose dehydrogeanse	UDP-glucose dehydrogeanse
4234	457	AB016536	(argininosuccinate lyase, heterogeneous nuclear ribonucleoprotein A/B)	(argininosuccinate lyase, heterogeneous nuclear ribonucleoprotein A/B)
23625	458	AB017260	solute carrier family 22, member 5	solute carrier family 22, member 5
15243	459	AB017912	MAD homolog 2 (Drosophila)	MAD homolog 2 (Drosophila)
18070	462	AF003008	max interacting protein 1	max interacting protein 1

Table 1				Atty. Ref. 44921-5133-WO
GLGC Identifier	SeqID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
7488	464	AF007758	synuclein, alpha	synuclein, alpha
1183	465	AF013144	MAP-kinase phosphatase (cpg21)	MAP-kinase phosphatase (cpg21)
16407	471	AF022247	cubilin	cubilin
25165	473	AF022952	vascular endothelial growth factor B	vascular endothelial growth factor B
3454	477	AF030091	cyclin L	cyclin L
23045	480	AF034218	hyaluronidase 2	hyaluronidase 2
8426	483	AF036335	NonO/p54nrb homolog	NonO/p54nrb homolog
17326	484	AF036548	Rgc32 protein	Rgc32 protein
17327	484	AF036548	Rgc32 protein	Rgc32 protein
22603	487	AF044574	2-4-dienoyl-Coenzyme A reductase 2, peroxisomal	2-4-dienoyl-Coenzyme A reductase 2, peroxisomal
20864	488	AF045464	aflatoxin B1 aldehyde reductase	aflatoxin B1 aldehyde reductase
10241	489	AF048687	UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 6	UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 6
117	490	AF049239	sodium channel, voltage-gated, type 8, alpha polypeptide	sodium channel, voltage-gated, type 8, alpha polypeptide
16649	491	AF051895	annexin 5	annexin 5
985	492	AF053312	small inducible cytokine subfamily A20	small inducible cytokine subfamily A20
4011	496	AF056333	cytochrome P450, subfamily 2E, polypeptide 1	cytochrome P450, subfamily 2E, polypeptide 1
1104	497	AF058714	solute carrier family 13, member 2	solute carrier family 13, member 2
4589	498	AF062389	kidney-specific protein (KS)	kidney-specific protein (KS)
16007	499	AF062594	nucleosome assembly protein 1-like 1	nucleosome assembly protein 1-like 1
16444	502	AF065438	peptidylprolyl isomerase C-associated protein	peptidylprolyl isomerase C-associated protein
16155	503	AF068860	defensin beta 1	defensin beta 1
25198	504	AF069782	Nopp140 associated protein	Nopp140 associated protein
744	506	AF076856	espin	espin
5496	507	AF080468	glucose-6-phosphatase, transport protein 1	glucose-6-phosphatase, transport protein 1
5497	507	AF080468	glucose-6-phosphatase, transport protein 1	glucose-6-phosphatase, transport protein 1
25204	508	AF080507		
17535	513	AF090306	retinoblastoma binding protein 7	retinoblastoma binding protein 7
16156	514	AF093536	defensin beta 1	defensin beta 1
4723	515	AF093773	malate dehydrogenase 1	malate dehydrogenase 1
2368	516	AF095741	Mg87 protein	Mg87 protein

Table 1				Atty. Ref: 44921-5133-WO
GLGC Identifier	Seq ID	GenBank Accor RefSeq ID	Known Gene Name	UniGene Cluster Title
2367	516	AF095741	Mg87 protein	Mg87 protein
6554	517	AF097723	plasma glutamate carboxypeptidase	plasma glutamate carboxypeptidase
15848	520	AI007820		Rattus norvegicus heat shock protein 90 beta mRNA, partial sequence
15849	523	AI008074		Rattus norvegicus heat shock protein 90 beta mRNA, partial sequence
15434	531	AI008836	high mobility group box 2	high mobility group box 2
15097	535	AI009405	insulin-like growth factor binding protein 3	insulin-like growth factor binding protein 3
23362	537	AI009605	Ras homolog enriched in brain	Ras homolog enriched in brain
17473	544	AI009806	dynein, cytoplasmic, light chain 1	dynein, cytoplasmic, light chain 1
15616	570	AI011998	dnaJ homolog, subfamily b, member 9	dnaJ homolog, subfamily b, member 9
20817	582	AI012589	(glutathione S-transferase, pi 2, glutathione-S-transferase, pi 1)	(glutathione S-transferase, pi 2, glutathione-S-transferase, pi 1)
18713	585	AI012604	eukaryotic initiation factor 5 (eIF-5)	eukaryotic initiation factor 5 (eIF-5)
21950	599	AI013861	3-hydroxyisobutyrate dehydrogenase	3-hydroxyisobutyrate dehydrogenase
815	603	AI014087	ribosomal protein S26	ribosomal protein S26
15247	606	AI014169	upregulated by 1,25-dihydroxyvitamin D-3	upregulated by 1,25-dihydroxyvitamin D-3
21682	635	AI045030	CCAAT/enhancerbinding, protein (C/EBP) delta	CCAAT/enhancerbinding, protein (C/EBP) delta
20802	655	AI059508	transketolase	transketolase
15190	705	AI102562	Metallothionein	Metallothionein
23837	707	AI102620		Rattus norvegicus transcribed sequences
4449	712	AI102838	Isovaleryl Coenzyme A dehydrogenase	Isovaleryl Coenzyme A dehydrogenase
15861	714	AI102868		Rattus norvegicus phosphoserine aminotransferase mRNA, complete cds
16918	715	AI103074	ribosomal protein S12	ribosomal protein S12
20833	731	AI104035		Rattus norvegicus transcribed sequence with strong similarity to protein ref:NP_079904.1 (M.musculus) RIKEN cDNA 2010000G05 [Mus musculus]
18077	740	AI105198	solute carrier family 34, member 1	solute carrier family 34, member 1
23660	747	AI105448	hydroxysteroid 11-beta dehydrogenase 1	hydroxysteroid 11-beta dehydrogenase 1
20919	756	AI112516	zinc finger protein 36, C3H type-like 1	zinc finger protein 36, C3H type-like 1
20920	763	AI136891	zinc finger protein 36, C3H type-like 1	zinc finger protein 36, C3H type-like 1
16510	771	AI137583		
17160	792	AI169370	alpha-tubulin	alpha-tubulin
8749	799	AI169802	ferritin, heavy polypeptide 1	ferritin, heavy polypeptide 1

Table 1 Atty Ref: 44921-5133.WO

GLGC Identifier	Seq ID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
18687	804	AI170568	dodecenoyl-coenzyme A delta isomerase	dodecenoyl-coenzyme A delta isomerase
21975	827	AI172247	xanthine dehydrogenase	xanthine dehydrogenase
21842	828	AI172293	sterol-C4-methyl oxidase-like	sterol-C4-methyl oxidase-like
15191	840	AI176456		Rattus norvegicus transcribed sequence with strong similarity to protein sp:P04355 (R.norvegicus) MT2_RAT METALLOTHIONEIN-II (MT-II)
20717	844	AI176504	glutaminase	glutaminase
16518	845	AI176546	heat shock protein 86	heat shock protein 86
3431	846	AI176595	Cathepsin L	Cathepsin L
17570	863	AI177683		Rattus norvegicus mRNA for hnRNP protein, partial
15259	870	AI178135	complement component 1, q subcomponent binding protein	complement component 1, q subcomponent binding protein
17563	875	AI178750	eukaryotic translation elongation factor 2	eukaryotic translation elongation factor 2
17829	884	AI179576	hemoglobin beta chain complex	hemoglobin beta chain complex
16081	888	AI179610	Heme oxygenase	Heme oxygenase
1474	903	AI228548		Rattus norvegicus transcribed sequence with strong similarity to protein sp:P35467 (R.norvegicus) S10A_RAT S-100 protein, alpha chain
15296	907	AI228738	(FK506 binding protein 2, FK506-binding protein 1a)	(FK506 binding protein 2, FK506-binding protein 1a)
17448	912	AI229637	MYB binding protein 1a	MYB binding protein 1a
15862	921	AI230228		Rattus norvegicus phosphoserine aminotransferase mRNA, complete cds
17196	942	AI231519	sialyltransferase 7c	sialyltransferase 7c
8212	945	AI231807	ferritin light chain 1	ferritin light chain 1
20702	946	AI231821	stathmin 1	stathmin 1
573	949	AI232087	hydroxyacid oxidase (glycolate oxidase) 3	hydroxyacid oxidase (glycolate oxidase) 3
409	953	AI232268	low density lipoprotein receptor-related protein associated protein 1	low density lipoprotein receptor-related protein associated protein 1
4574	968	AI233216	glutamate dehydrogenase 1	glutamate dehydrogenase 1
17764	985	AI234604	heat shock protein 8	heat shock protein 8
15468	997	AI235364	ribosomal protein S15a	ribosomal protein S15a
15850	1018	AI236795		Rattus norvegicus heat shock protein 90 beta mRNA, partial sequence
11692	1027	AI638982	sulfotransferase family, cytosolic, 1C, member 2	sulfotransferase family, cytosolic, 1C, member 2
19997	1031	AI639043		Rattus norvegicus transcribed sequences

Table 1 Atty Ref: 44921-5133.WO

GLGC Identifier	Seq ID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
10071	1032	AI639058		Rattus norvegicus transcribed sequence with strong similarity to protein ref:NP_075371.1 (M.musculus) Nedd4 WW binding# protein 4; Nedd4 WW-binding protein 4 [Mus musculus]
16676	1033	AI639082	mini chromosome maintenance deficient 6 (S. cerevisiae)	mini chromosome maintenance deficient 6 (S. cerevisiae)
19952	1034	AI639108		Rattus norvegicus transcribed sequences
15379	1037	AI639162		Rattus norvegicus transcribed sequences
25907	1038	AI639167		Rattus norvegicus transcribed sequences
19002	1043	AI639465	ring finger protein 28	ring finger protein 28
19943	1045	AI639479		Rattus norvegicus transcribed sequence with strong similarity to protein prf:2008147A (R.norvegicus) 2008147A protein RAKb [Rattus norvegicus]
20082	1046	AI639488		Rattus norvegicus transcribed sequence with strong similarity to protein pir:A42772 (R.norvegicus) A42772 mdm2 protein - rat (fragments)
1203	1049	AJ000485	cytoplasmic linker 2	cytoplasmic linker 2
12422	1053	AJ006971	Death-associated like kinase	Death-associated like kinase
12423	1053	AJ006971	Death-associated like kinase	Death-associated like kinase
25247	1054	AJ011608	DNA primase, p49 subunit	DNA primase, p49 subunit
20404	1055	AJ011656	claudin 3	claudin 3
18956	1059	D00512	acetyl-coenzyme A acetyltransferase 1	acetyl-coenzyme A acetyltransferase 1
15409	1060	D00569	2,4-dienoyl CoA reductase 1, mitochondrial	2,4-dienoyl CoA reductase 1, mitochondrial
15408	1060	D00569	2,4-dienoyl CoA reductase 1, mitochondrial	2,4-dienoyl CoA reductase 1, mitochondrial
4615	1061	D00680	glutathione peroxidase 3	glutathione peroxidase 3
18686	1062	D00729	dodecenoyl-coenzyme A delta isomerase	(Rattus norvegicus mRNA for delta3, delta2-enoyl-CoA isomerase, complete cds, dodecenoyl-coenzyme A delta isomerase)
2554	1063	D00913	intercellular adhesion molecule 1	intercellular adhesion molecule 1
1306	1065	D10262	choline kinase	choline kinase
3254	1070	D10756	proteasome (prosome, macropain) subunit, alpha type 5	proteasome (prosome, macropain) subunit, alpha type 5
4003	1071	D10757	proteosome (prosome, macropain) subunit, beta type 9 (large multifunctional protease 2)	proteosome (prosome, macropain) subunit, beta type 9 (large multifunctional protease 2)
23109	1072	D10854	aldo-keto reductase family 1, member A1	aldo-keto reductase family 1, member A1
24428	1074	D13126	neural visinin-like Ca2+-binding protein type 3	neural visinin-like Ca2+-binding protein type 3
15281	1075	D13623		

Table 1 Atty Ref: 44921-5133-WO

GLGC Identifier	Seq ID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
25257	1075	D13623		
1214	1076	D13871	(nuclear receptor subfamily 1, group H, member 4, solute carrier family 2, member 5)	(nuclear receptor subfamily 1, group H, member 4, solute carrier family 2, member 5)
18958	1077	D13921	acetyl-coenzyme A acetyltransferase 1	acetyl-coenzyme A acetyltransferase 1
18727	1078	D13978	argininosuccinate lyase	argininosuccinate lyase
11434	1079	D14014	cyclin D1	cyclin D1
18246	1081	D14441	brain acidic membrane protein	brain acidic membrane protein
16768	1083	D16478	hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A hiolase/enoyl-Coenzyme A hydratase (trifunctional protein), alpha subunit	hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A hiolase/enoyl-Coenzyme A hydratase (trifunctional protein), alpha subunit
18452	1085	D17370	CTL target antigen	CTL target antigen
18453	1085	D17370	CTL target antigen	CTL target antigen
16683	1086	D17445	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta polypeptide	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta polypeptide
24885	1088	D25224	laminin receptor 1 (67kD, ribosomal protein SA)	laminin receptor 1 (67kD, ribosomal protein SA)
20493	1090	D28339	3-hydroxyanthranilate 3,4-dioxygenase	3-hydroxyanthranilate 3,4-dioxygenase
16610	1091	D28557	cold shock domain protein A	cold shock domain protein A
16681	1095	D37920	squalene epoxidase	squalene epoxidase
5492	1097	D38061	UDP glycosyltransferase 1 family, polypeptide A6	UDP glycosyltransferase 1 family, polypeptide A6
18028	1098	D38062	UDP glycosyltransferase 1 family, polypeptide A7	UDP glycosyltransferase 1 family, polypeptide A7
1354	1099	D38065	UDP glycosyltransferase 1 family, polypeptide A1	UDP glycosyltransferase 1 family, polypeptide A1
755	1100	D38448	diacylglycerol kinase, gamma	diacylglycerol kinase, gamma
25290	1102	D42148	growth arrest specific 6	growth arrest specific 6
20494	1103	D44494	3-hydroxyanthranilate 3,4-dioxygenase	3-hydroxyanthranilate 3,4-dioxygenase
20801	1104	D44495	apurinic/apyrimidinic endonuclease 1	apurinic/apyrimidinic endonuclease 1
18750	1105	D45250	protease (prosome, macropain) 28 subunit, beta	protease (prosome, macropain) 28 subunit, beta
16354	1108	D50564	mercaptopyruvate sulfurtransferase	mercaptopyruvate sulfurtransferase
770	1112	D83044	solute carrier family 22, member 2	solute carrier family 22, member 2

Table 1 — Atty Ref: 44921-5133.WO

GLGC# identifier	Seq ID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
15126	1113	D83796	(UDP glycosyltransferase 1 family, polypeptide A1, UDP glycosyltransferase 1 family, polypeptide A6, UDP glycosyltransferase 1 family, polypeptide A7, UDP-glucuronosyltransferase 1A8)	(UDP glycosyltransferase 1 family, polypeptide A1, UDP glycosyltransferase 1 family, polypeptide A6, UDP glycosyltransferase 1 family, polypeptide A7, UDP-glucuronosyltransferase 1A8)
17554	1115	D85100	solute carrier family 27 (fatty acid transporter), member 32	solute carrier family 27 (fatty acid transporter), member 32
13005	1116	D85189	fatty acid Coenzyme A ligase, long chain 4	fatty acid Coenzyme A ligase, long chain 4
16448	1117	D86297	aminolevulinic acid synthase 2	aminolevulinic acid synthase 2
15297	1118	D86641	(FK506 binding protein 2, FK506-binding protein 1a)	(FK506 binding protein 2, FK506-binding protein 1a)
945	1120	D88666	phosphatidylserine-specific phospholipase A1	phosphatidylserine-specific phospholipase A1
25315	1121	D89730		
3987	1122	D90258	proteasome (prosome, macropain) subunit, alpha type 3	proteasome (prosome, macropain) subunit, alpha type 3
1921	1123	E01524	P450 (cytochrome) oxidoreductase	P450 (cytochrome) oxidoreductase
25024	1124	E03229	cytosolic cysteine dioxygenase 1	cytosolic cysteine dioxygenase 1
19824	1125	E13557	cysteine-sulfinate decarboxylase	cysteine-sulfinate decarboxylase
4361	1127	H31839	BCL2-antagonist/killer 1	BCL2-antagonist/killer 1
21011	1128	H32189	glutathione S-transferase, mu 1	glutathione S-transferase, mu 1
4386	1129	H33093		Rattus norvegicus transcribed sequences
1301	1132	J02585	stearoyl-Coenzyme A desaturase 1	stearoyl-Coenzyme A desaturase 1
21012	1133	J02592	Glutathione-S-transferase, mu type 2 (Yb2)	Glutathione-S-transferase, mu type 2 (Yb2)
15124	1134	J02612	(UDP glycosyltransferase 1 family, polypeptide A1, UDP glycosyltransferase 1 family, polypeptide A6, UDP glycosyltransferase 1 family, polypeptide A7, UDP-glucuronosyltransferase 1A8)	(UDP glycosyltransferase 1 family, polypeptide A1, UDP glycosyltransferase 1 family, polypeptide A6, UDP glycosyltransferase 1 family, polypeptide A7, UDP-glucuronosyltransferase 1A8)
1174	1136	J02657	Cytochrome P450, subfamily IIC (mephenytoin 4-hydroxylase)	Cytochrome P450, subfamily IIC (mephenytoin 4-hydroxylase)
16080	1138	J02722	Heme oxygenase	Heme oxygenase
23699	1139	J02749	acetyl-Coenzyme A acyltransferase 1 (peroxisomal 3-oxoacyl-Coenzyme A thiolase)	acetyl-Coenzyme A acyltransferase 1 (peroxisomal 3-oxoacyl-Coenzyme A thiolase)
23698	1139	J02749	acetyl-Coenzyme A acyltransferase 1 (peroxisomal 3-oxoacyl-Coenzyme A thiolase)	acetyl-Coenzyme A acyltransferase 1 (peroxisomal 3-oxoacyl-Coenzyme A thiolase)
16148	1140	J02752	acyl-coA oxidase	acyl-coA oxidase

Table 1				Atty. Ref. 44921-5133-WO
GLGC Identifier	Seq ID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
1514	1142	J02780	Tropomycin 4	Tropomycin 4
21078	1143	J02791	acetyl-coenzyme A dehydrogenase, medium chain	acetyl-coenzyme A dehydrogenase, medium chain
21013	1144	J02810	glutathione S-transferase, mu 1	glutathione S-transferase, mu 1
17284	1145	J02827	branched chain keto acid dehydrogenase subunit E1, alpha polypeptide	branched chain keto acid dehydrogenase subunit E1, alpha polypeptide
17285	1145	J02827	branched chain keto acid dehydrogenase subunit E1, alpha polypeptide	branched chain keto acid dehydrogenase subunit E1, alpha polypeptide
1762	1147	J03179	D site albumin promoter binding protein	D site albumin promoter binding protein
1763	1147	J03179	D site albumin promoter binding protein	D site albumin promoter binding protein
13479	1149	J03481	quinoid dihydropteridine reductase	quinoid dihydropteridine reductase
13480	1149	J03481	quinoid dihydropteridine reductase	quinoid dihydropteridine reductase
14997	1150	J03572	alkaline phosphatase, tissue-nonspecific	alkaline phosphatase, tissue-nonspecific
16948	1151	J03588	Guanidinoacetate methyltransferase	Guanidinoacetate methyltransferase
15017	1153	J03752	microsomal glutathione S-transferase 1	microsomal glutathione S-transferase 1
17394	1156	J03969	nucleophosmin 1	nucleophosmin 1
7784	1157	J04591	Dipeptidyl peptidase 4	Dipeptidyl peptidase 4
23524	1158	J04792		
17393	1159	J04943	nucleophosmin 1	nucleophosmin 1
6780	1160	J05029	acetyl-Coenzyme A dehydrogenase, long-chain	acetyl-Coenzyme A dehydrogenase, long-chain
4451	1161	J05031	Isovaleryl Coenzyme A dehydrogenase	Isovaleryl Coenzyme A dehydrogenase
4450	1161	J05031	Isovaleryl Coenzyme A dehydrogenase	Isovaleryl Coenzyme A dehydrogenase
15125	1162	J05132	(UDP glycosyltransferase 1 family, polypeptide A1, UDP glycosyltransferase 1 family, polypeptide A6, UDP glycosyltransferase 1 family, polypeptide A7, UDP-glucuronosyltransferase 1A8)	(UDP glycosyltransferase 1 family, polypeptide A1, UDP glycosyltransferase 1 family, polypeptide A6, UDP glycosyltransferase 1 family, polypeptide A7, UDP-glucuronosyltransferase 1A8)
1247	1163	J05181	glutamate-cysteine ligase catalytic subunit	glutamate-cysteine ligase catalytic subunit
1977	1164	J05470	Carnitine palmitoyltransferase 2	Carnitine palmitoyltransferase 2
24563	1167	J05592	protein phosphatase 1, regulatory (inhibitor) subunit 1A	protein phosphatase 1, regulatory (inhibitor) subunit 1A
24564	1167	J05592	protein phosphatase 1, regulatory (inhibitor) subunit 1A	protein phosphatase 1, regulatory (inhibitor) subunit 1A
18989	1168	K00136	glutathione-S-transferase, alpha type2	glutathione-S-transferase, alpha type2
634	1170	K01932	glutathione S-transferase, alpha 1	glutathione S-transferase, alpha 1

Table 1				Atty. Ref.: 44921-5133-WO
GLGC Identifier	Seq ID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
20149	1172	K03243		
17758	1173	K03249	enoyl-Coenzyme A, hydratase/3-hydroxyacyl Coenzyme A dehydrogenase	enoyl-Coenzyme A, hydratase/3-hydroxyacyl Coenzyme A dehydrogenase
10878	1174	K03250	ribosomal protein S11	ribosomal protein S11
20865	1175	L00117	Elastase 1	Elastase 1
1894	1176	L03201	cathepsin S	cathepsin S
15411	1178	L07736	carnitine palmitoyltransferase 1	carnitine palmitoyltransferase 1
617	1179	L08831	Glucose-dependent insulinotropic peptide	Glucose-dependent insulinotropic peptide
3549	1181	L11319	signal peptidase complex 18kD	signal peptidase complex 18kD
22412	1184	L13619	growth response protein (CL-6)	growth response protein (CL-6)
22413	1184	L13619	growth response protein (CL-6)	growth response protein (CL-6)
109	1187	L14004	Polymeric immunoglobulin receptor	Polymeric immunoglobulin receptor
1475	1190	L16764	heat shock 70kD protein 1A	heat shock 70kD protein 1A
24770	1191	L19031	solute carrier family 21, member 1	solute carrier family 21, member 1
4749	1192	L19998	sulfotransferase family 1A, phenol-preferring, member 1	sulfotransferase family 1A, phenol-preferring, member 1
4748	1192	L19998	sulfotransferase family 1A, phenol-preferring, member 1	sulfotransferase family 1A, phenol-preferring, member 1
10248	1193	L23148	inhibitor of DNA binding 1, helix-loop-helix protein (splice variation)	Inhibitor of DNA binding 1, helix-loop-helix protein (splice variation)
43	1194	L23413	solute carrier family 26 (sulfate transporter), member 1	solute carrier family 26 (sulfate transporter), member 1
22411	1198	L26292	Kruppel-like factor 4 (gut)	Kruppel-like factor 4 (gut)
15872	1201	L28135	solute carrier family 2, member 2	solute carrier family 2, member 2
15112	1205	L34049	low density lipoprotein receptor-related protein 2	low density lipoprotein receptor-related protein 2
1321	1206	L37333	glucose-6-phosphatase, catalytic	glucose-6-phosphatase, catalytic
13682	1207	L38482		
6406	1208	L38615	glutathione synthetase	glutathione synthetase
1427	1209	L38644	karyopherin,beta 1	karyopherin,beta 1
11955	1212	L48209	cytochrome c oxidase, subunit VIIIa	cytochrome c oxidase, subunit VIIIa
1920	1213	M10068	P450 (cytochrome) oxidoreductase	P450 (cytochrome) oxidoreductase
15741	1214	M11670	Catalase	Catalase
15189	1215	M11794	Metallothionein	Metallothionein
17765	1216	M11942	heat shock protein 8	heat shock protein 8

Table 1				Atty. Ref. 44921-5133-WO
GLGC Identifier	Seq ID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
17502	1217	M12156	heterogeneous nuclear ribonucleoprotein A1	heterogeneous nuclear ribonucleoprotein A1
6055	1218	M12337	Phenylalanine hydroxylase	Phenylalanine hydroxylase
4254	1219	M12450	Group-specific component (vitamin D-binding protein)	Group-specific component (vitamin D-binding protein)
7064	1220	M12919	aldolase A	aldolase A
1466	1222	M14050	heat shock 70kD protein 5	heat shock 70kD protein 5
455	1225	M15474	tropomyosin 1, alpha	tropomyosin 1, alpha
19255	1227	M15562		Rat MHC class II RT1.u-D-alpha chain mRNA, 3' end
19256	1227	M15562		Rat MHC class II RT1.u-D-alpha chain mRNA, 3' end
20809	1229	M17069	Calmodulin 2 (phosphorylase kinase, delta)	Calmodulin 2 (phosphorylase kinase, delta)
25405	1230	M18330	protein kinase C, delta	protein kinase C, delta
24567	1234	M19304	prolactin receptor	prolactin receptor
17198	1235	M19647	kallikrein 1	kallikrein 1
17197	1235	M19647		
4010	1237	M20131		
20481	1240	M22631	Propionyl Coenzyme A carboxylase, alpha polypeptide	Propionyl Coenzyme A carboxylase, alpha polypeptide
46	1242	M23697	Plasminogen activator, tissue	Plasminogen activator, tissue
18619	1244	M24324	RT1 class Ib gene	RT1 class Ib gene
1540	1246	M25073	alanyl (membrane) aminopeptidase	alanyl (membrane) aminopeptidase
17541	1247	M26125	epoxide hydrolase 1	epoxide hydrolase 1
23225	1249	M27467	cytochrome oxidase subunit VIc	cytochrome oxidase subunit VIc
11956	1250	M28255	cytochrome c oxidase, subunit VIIIa	cytochrome c oxidase, subunit VIIIa
17105	1251	M29358	ribosomal protein S6	ribosomal protein S6
14346	1252	M31109	UDP-glucuronosyltransferase 2B3 precursor, microsomal	UDP-glucuronosyltransferase 2B3 precursor, microsomal
1814	1253	M31174	thyroid hormone receptor alpha	thyroid hormone receptor alpha
18502	1254	M31178	calbindin 1	calbindin 1
18501	1254	M31178	calbindin 1	calbindin 1
20868	1256	M32062	Fc receptor, IgG, low affinity III	Fc receptor, IgG, low affinity III
20869	1256	M32062	Fc receptor, IgG, low affinity III	Fc receptor, IgG, low affinity III
20298	1257	M32783		
15580	1258	M33648	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2
11755	1259	M33746	UDP-glucuronosyltransferase 2 family, member 5	UDP-glucuronosyltransferase 2 family, member 5

Table 1 Atty. Ref. 44921-5133.WO

GLGC Identifier	Seq ID	GenBank Accor. RefSeq ID	Known Gene Name	UniGene Cluster Title
20126	1263	M34253	Interferon regulatory factor 1	Interferon regulatory factor 1
24590	1264	M35299	serine protease inhibitor, Kazal type 1	serine protease inhibitor, Kazal type 1
20699	1265	M35601	Fibrinogen, A alpha polypeptide	Fibrinogen, A alpha polypeptide
20700	1265	M35601	Fibrinogen, A alpha polypeptide	Fibrinogen, A alpha polypeptide
17661	1267	M37584	H2A histone family, member Z	H2A histone family, member Z
9109	1269	M38135	Cathepsin H	Cathepsin H
13723	1272	M55534	crystallin, alpha B	crystallin, alpha B
4467	1274	M57664	creatine kinase, brain	creatine kinase, brain
20713	1275	M57718	cytochrome P450,4A1	cytochrome P450,4A1
25057	1277	M58495		
12606	1281	M59861	10-formyltetrahydrofolate dehydrogenase	10-formyltetrahydrofolate dehydrogenase
17378	1284	M62388	ubiquitin conjugating enzyme	ubiquitin conjugating enzyme
14956	1286	M64301	mitogen-activated protein kinase 6	mitogen-activated protein kinase 6
14957	1286	M64301	mitogen-activated protein kinase 6	mitogen-activated protein kinase 6
19825	1288	M64755	cysteine-sulfinate decarboxylase	cysteine-sulfinate decarboxylase
17301	1292	M69246	serine (or cysteine) proteinase inhibitor, clade H, member 1	serine (or cysteine) proteinase inhibitor, clade H, member 1
24648	1294	M74054	angiotensin receptor 1a	angiotensin receptor 1a
20405	1295	M74067	claudin 3	claudin 3
240	1297	M75153	RAB11a, member RAS oncogene family	RAB11a, member RAS oncogene family
23961	1298	M77694	fumarylacetoacetate hydrolase	fumarylacetoacetate hydrolase
1622	1300	M80804	solute carrier family 3, member 1	solute carrier family 3, member 1
24843	1301	M80826	trefoil factor 3	trefoil factor 3
5733	1303	M81855	(ATP-binding cassette, sub-family B (MDR/TAP), member 1A, P-glycoprotein/multidrug resistance 1)	(ATP-binding cassette, sub-family B (MDR/TAP), member 1A, P-glycoprotein/multidrug resistance 1)
17149	1304	M83107	Transgelin (Smooth muscle 22 protein)	Transgelin (Smooth muscle 22 protein)
17150	1304	M83107	Transgelin (Smooth muscle 22 protein)	Transgelin (Smooth muscle 22 protein)
4198	1305	M83143	Sialyltransferase 1 (beta-galactoside alpha-2,6-sialytransferase)	Sialyltransferase 1 (beta-galactoside alpha-2,6-sialytransferase)
4199	1305	M83143	Sialyltransferase 1 (beta-galactoside alpha-2,6-sialytransferase)	Sialyltransferase 1 (beta-galactoside alpha-2,6-sialytransferase)

Table 1				Atty. Ref. 44921-5133.WO
GLGC Identifier	Seq ID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
24651	1306	M83678	RAB13	RAB13
21882	1308	M83740	6-pyruvoyl-tetrahydropterin synthase/dimerization cofactor of hepatocyte nuclear factor 1 alpha	6-pyruvoyl-tetrahydropterin synthase/dimerization cofactor of hepatocyte nuclear factor 1 alpha
23445	1310	M84719	Flavin-containing monooxygenase 1	Flavin-containing monooxygenase 1
24438	1311	M85183	angiotensin/vasopressin receptor	angiotensin/vasopressin receptor
24496	1312	M85300	solute carrier family 9, member 3	solute carrier family 9, member 3
16895	1313	M86240	fructose-1,6- biphosphatase 1	fructose-1,6- biphosphatase 1
7872	1315	M86912		
291	1316	M88347	Cystathionine beta synthase	Cystathionine beta synthase
24615	1318	M89646	ribosomal protein S24	ribosomal protein S24
25460	1319	M89945	farensyl diphosphate synthase	farensyl diphosphate synthase
11153	1320	M91652	glutamine synthetase 1	glutamine synthetase 1
25467	1321	M93297	ornithine aminotransferase	ornithine aminotransferase
25468	1324	M94918	hemoglobin beta chain complex	hemoglobin beta chain complex
25469	1325	M94919		
1976	1326	M95493	guanylate cyclase activator 2A	guanylate cyclase activator 2A
16449	1327	M95591	farnesyl diphosphate farnesyl transferase 1	farnesyl diphosphate farnesyl transferase 1
16450	1327	M95591	farnesyl diphosphate farnesyl transferase 1	farnesyl diphosphate farnesyl transferase 1
729	1328	M95762	solute carrier family 6 (neurotransmitter transporter, GABA), member 13	solute carrier family 6 (neurotransmitter transporter, GABA), member 13
1678	1331	M96674	glucagon receptor	glucagon receptor
1508	1332	M97662	ureidopropionase, beta	ureidopropionase, beta
23708	1335	NM_013113	ATPase Na+/K+ transporting beta 1 polypeptide	ATPase Na+/K+ transporting beta 1 polypeptide
754	1336	NM_013126	diacylglycerol kinase, gamma	diacylglycerol kinase, gamma
13938	1339	NM_017212	microtubule-associated protein tau	microtubule-associated protein tau
1729	1342	NM_019147	jagged 1	jagged 1
15201	1349	NM_031093		
18008	1350	NM_031588	neuregulin 1	neuregulin 1
16726	1352	NM_031855	Ketohexokinase	Ketohexokinase
23709	1356	NM_138532	(ATPase Na+/K+ transporting beta 1 polypeptide, NME7)	(ATPase Na+/K+ transporting beta 1 polypeptide, NME7)
20795	1360	NM_175761	heat shock protein 86	heat shock protein 86

Table 1				Atty. Ref. 44921-5133.WO
GLGC Identifier	SeqID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
5837	1363	S43408	Meprin 1 alpha	Meprin 1 alpha
25064	1364	S45392		
25480	1365	S46785	insulin-like growth factor binding protein, acid labile subunit	insulin-like growth factor binding protein, acid labile subunit
25481	1366	S46798		
4012	1367	S48325	cytochrome P450, subfamily 2E, polypeptide 1	cytochrome P450, subfamily 2E, polypeptide 1
10886	1368	S49003		
5493	1369	S56936	UDP glycosyltransferase 1 family, polypeptide A6	UDP glycosyltransferase 1 family, polypeptide A6
15127	1370	S56937	(UDP glycosyltransferase 1 family, polypeptide A1, UDP glycosyltransferase 1 family, polypeptide A6, UDP glycosyltransferase 1 family, polypeptide A7, UDP-glucuronosyltransferase 1A8)	(UDP glycosyltransferase 1 family, polypeptide A1, UDP glycosyltransferase 1 family, polypeptide A6, UDP glycosyltransferase 1 family, polypeptide A7, UDP-glucuronosyltransferase 1A8)
14003	1374	S65555	glutamate cysteine ligase, modifier subunit	glutamate cysteine ligase, modifier subunit
355	1375	S66024	cAMP responsive element modulator	cAMP responsive element modulator
356	1375	S66024	cAMP responsive element modulator	cAMP responsive element modulator
16248	1376	S68135	solute carrier family 2,member 1	solute carrier family 2,member 1
15832	1377	S68589		
1471	1378	S68809	S100 calcium binding protein A1	
18647	1379	S69316	tumor rejection antigen gp96	
9224	1381	S70011		
25518	1381	S70011		
15135	1382	S71021	ribosomal protein L6	ribosomal protein L6
25525	1383	S72505	glutathione S-transferase, alpha 1	glutathione S-transferase, alpha 1
18990	1384	S72506		
16211	1386	S75960	uromodulin	uromodulin
1943	1388	S77494	lysyl oxidase	lysyl oxidase
21583	1389	S77900		
25545	1389	S77900		
25546	1390	S78154		
10260	1393	S81497	lipase A, lysosomal acid	lipase A, lysosomal acid
25563	1393	S81497	lipase A, lysosomal acid	lipase A, lysosomal acid
14121	1394	S82383	tropomyosin isoform 6	tropomyosin isoform 6

Table 1				Atty. Ref 44921-5133-WO
GLGC Identifier	Seq ID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
3609	1395	S82579	histamine N-methyltransferase	histamine N-methyltransferase
25069	1396	S82820		
25070	1397	S83279	peroxisomal multifunctional enzyme type II	peroxisomal multifunctional enzyme type II
18005	1401	U02320	neuregulin 1	neuregulin 1
20885	1403	U04842	epidermal growth factor	epidermal growth factor
23606	1406	U05784	microtubule-associated proteins 1A/1B light chain 3	microtubule-associated proteins 1A/1B light chain 3
17806	1407	U06273	UDP-glucuronosyltransferase	UDP-glucuronosyltransferase
17805	1408	U06274	UDP-glucuronosyltransferase	UDP-glucuronosyltransferase
24874	1410	U07619	coagulation factor 3	coagulation factor 3
20925	1412	U08976	enoyl coenzyme A hydratase 1	enoyl coenzyme A hydratase 1
20803	1413	U09256	transketolase	transketolase
646	1415	U10097	solute carrier family 12, member 3	solute carrier family 12, member 3
714	1416	U10279	solute carrier family 28 (sodium-coupled nucleoside transporter), member 1	solute carrier family 28 (sodium-coupled nucleoside transporter), member 1
1929	1418	U10357	pyruvate dehydrogenase kinase 2	pyruvate dehydrogenase kinase 2
1928	1418	U10357	pyruvate dehydrogenase kinase 2	pyruvate dehydrogenase kinase 2
16268	1419	U10894	(allograft inflammatory factor 1, balloon angioplasty responsive transcript)	(allograft inflammatory factor 1, balloon angioplasty responsive transcript)
24900	1420	U12973	X transporter protein 2	X transporter protein 2
1424	1423	U14746	von Hippel-Lindau syndrome homolog	von Hippel-Lindau syndrome homolog
16675	1425	U17565	mini chromosome maintenance deficient 6 (S. cerevisiae)	mini chromosome maintenance deficient 6 (S. cerevisiae)
16871	1428	U18314	thymopoietin	thymopoietin
22196	1433	U21719		Rattus norvegicus clone D920 intestinal epithelium proliferating cell-associated mRNA sequence
133	1436	U24174	cyclin-dependent kinase inhibitor 1A	cyclin-dependent kinase inhibitor 1A
1537	1441	U27518	UDP-glucuronosyltransferase	UDP-glucuronosyltransferase
1558	1442	U28504	solute carrier family 17 vesicular glutamate transporter), member 1	solute carrier family 17 vesicular glutamate transporter), member 1
1559	1442	U28504	solute carrier family 17 vesicular glutamate transporter), member 1	solute carrier family 17 vesicular glutamate transporter), member 1
20780	1444	U29881	low affinity Na-dependent glucose transporter (SGLT2)	low affinity Na-dependent glucose transporter (SGLT2)

Table 1				Atty. Ref. 44921-5133.WO
GLGC Identifier	SeqID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
1598	1445	U30186	DNA-damage inducible transcript 3	DNA-damage inducible transcript 3
1970	1446	U31463	myosin, heavy polypeptide 9	myosin, heavy polypeptide 9
1479	1447	U32314	Pyruvate carboxylase	Pyruvate carboxylase
23826	1451	U38180	solute carrier family 19, member 1	solute carrier family 19, member 1
797	1452	U38253	eukaryotic translation initiation factor 2B, subunit 3 (gamma, 58kD)	eukaryotic translation initiation factor 2B, subunit 3 (gamma, 58kD)
19543	1455	U44948	cysteine rich protein 2	cysteine rich protein 2
16147	1459	U51898	phospholipase A2, group VI	phospholipase A2, group VI
12014	1462	U54632	Ubiquitin conjugating enzyme E2I	Ubiquitin conjugating enzyme E2I
989	1464	U56242	v-maf musculoaponeurotic fibrosarcoma (avian) oncogene homolog (c-maf)	v-maf musculoaponeurotic fibrosarcoma (avian) oncogene homolog (c-maf)
16708	1465	U57042	adenosine kinase	adenosine kinase
912	1468	U59184	bcl2-associated X protein	bcl2-associated X protein
15174	1469	U59809	insulin-like growth factor 2 receptor	insulin-like growth factor 2 receptor
20772	1470	U60882	heterogeneous nuclear ribonucleoproteins methyltransferase-like 2 (S. cerevisiae)	heterogeneous nuclear ribonucleoproteins methyltransferase-like 2 (S. cerevisiae)
24643	1477	U68417	branched chain aminotransferase 2, mitochondrial	branched chain aminotransferase 2, mitochondrial
16398	1478	U75392	B-cell receptor-associated protein 37	B-cell receptor-associated protein 37
25632	1481	U75405	collagen, type 1, alpha 1	collagen, type 1, alpha 1
1602	1483	U76379	solute carrier family 22, member 1	solute carrier family 22, member 1
20887	1484	U76635	Deoxyribonuclease I	Deoxyribonuclease I
4957	1485	U76714	solute carrier family 39 (iron-regulated transporter), member 1	solute carrier family 39 (iron-regulated transporter), member 1
25643	1486	U77829	growth arrest specific 5	growth arrest specific 5
23300	1488	U84727	2-oxoglutarate carrier	2-oxoglutarate carrier
1546	1489	U85512	GTP cyclohydrolase I feedback regulatory protein	GTP cyclohydrolase I feedback regulatory protein
1419	1492	U90887	arginase 2	arginase 2
22675	1493	U92081	glycoprotein 38	glycoprotein 38
17158	1496	V01227	alpha-tubulin	alpha-tubulin
818	1497	X02291	aldolase B	aldolase B

Table 1				Atty. Ref: 44921-5133-WO
GLGC Identifier	Seq ID	GenBank Acc or RefSeq ID	Known Gene Name	UniGene Cluster Title
20818	1498	X02904	(glutathione S-transferase, pi 2, glutathione-S-transferase, pi 1)	(glutathione S-transferase, pi 2, glutathione-S-transferase, pi 1)
33	1500	X03518	gamma-glutamyl transpeptidase	gamma-glutamyl transpeptidase
20513	1503	X05684	pyruvate kinase, liver and RBC	pyruvate kinase, liver and RBC
1551	1504	X06150	Glycine methyltransferase	Glycine methyltransferase
1550	1504	X06150	Glycine methyltransferase	Glycine methyltransferase
16204	1505	X06423	ribosomal protein S8	ribosomal protein S8
16205	1505	X06423	ribosomal protein S8	ribosomal protein S8
20715	1507	X07259	cytochrome P450,4A1	cytochrome P450,4A1
23523	1509	X07944	ornithine decarboxylase 1	ornithine decarboxylase 1
16947	1510	X08056	Guanidinoacetate methyltransferase	Guanidinoacetate methyltransferase
1853	1511	X12367	Glutathione peroxidase 1	
20597	1512	X12459	arginosuccinate synthetase	arginosuccinate synthetase
20884	1513	X12748	epidermal growth factor	epidermal growth factor
17377	1514	X13058	tumor protein p53	tumor protein p53
24778	1515	X13119	serine dehydratase	serine dehydratase
16847	1516	X13549	ribosomal protein S10	ribosomal protein S10
20810	1517	X14181		
25675	1517	X14181		
15653	1518	X14210	ribosomal protein S4, X-linked	
25676	1519	X14254		
20518	1520	X14265	calmodulin 3	calmodulin 3
19244	1521	X15013		
1069	1522	X15096	acidic ribosomal protein P0	acidic ribosomal protein P0
20483	1524	X15939	myosin heavy chain, polypeptide 7	myosin heavy chain, polypeptide 7
21562	1525	X15958	enoyl Coenzyme A hydratase, short chain 1	enoyl Coenzyme A hydratase, short chain 1
3202	1527	X16043	Protein phosphatase 2 (formerly 2A), catalytic subunit, alpha isoform	Protein phosphatase 2 (formerly 2A), catalytic subunit, alpha isoform
25682	1530	X16933	RNA binding protein p45AUF1	RNA binding protein p45AUF1
25686	1532	X51536	ribosomal protein S3	
23987	1533	X51615		

Table 1 Atty. Ref. 44921-5133-WO

GLGC Identifier	Seq ID	GenBank Accor RefSeq ID	Known Gene Name	UniGene Cluster Title
20872	1534	X51707	ribosomal protein S19	
9620	1535	X53377	ribosomal protein S7	ribosomal protein S7
20427	1536	X53378	ribosomal protein S13	ribosomal protein S13
25691	1537	X53504		
12903	1538	X53517	CD37 antigen	CD37 antigen
21122	1546	X56228	thiosulfate sulfurtransferase	thiosulfate sulfurtransferase
21123	1546	X56228	thiosulfate sulfurtransferase	thiosulfate sulfurtransferase
1885	1548	X56546	transcription factor 2	transcription factor 2
10860	1549	X57133	hepatocyte nuclear factor 4, alpha	hepatocyte nuclear factor 4, alpha
25699	1549	X57133	hepatocyte nuclear factor 4, alpha	hepatocyte nuclear factor 4, alpha
10267	1550	X57432	ribosomal protein S2	ribosomal protein S2
1037	1551	X57523	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)
5667	1553	X58200	ribosomal protein L23	
18611	1553	X58200	ribosomal protein L23	
17175	1554	X58389		
10109	1555	X58465	ribosomal protein S5	
25702	1555	X58465	ribosomal protein S5	
25707	1558	X59677	solute carrier family 13, member 2	solute carrier family 13, member 2
21651	1560	X60767	cell division cycle 2 homolog A (S. pombe)	cell division cycle 2 homolog A (S. pombe)
15875	1563	X62145	ribosomal protein L8	
4441	1564	X62146		
25719	1564	X62146		
13646	1565	X62166		
18108	1566	X62528	ribonuclease/angiogenin inhibitor	ribonuclease/angiogenin inhibitor
556	1569	X64336	Protein C	Protein C
20844	1570	X65228		
417	1574	X70141		
24640	1576	X70521	Sodium channel, nonvoltage-gated 1, alpha (epithelial)	Sodium channel, nonvoltage-gated 1, alpha (epithelial)
22219	1578	X72792	alcohol dehydrogenase 1	alcohol dehydrogenase 1
24626	1581	X75856	Testis enhanced gene transcript	Testis enhanced gene transcript

Table 1 Atty. Ref. 44921-5133-WO

GLGC Identifier	Seq ID	GenBank Accor. RefSeq ID	Known Gene Name	UniGene Cluster Title
16272	1582	X76456	afamin	afamin
24639	1584	X77932	Sodium channel, nonvoltage-gated 1, beta (epithelial)	Sodium channel, nonvoltage-gated 1, beta (epithelial)
23854	1585	X78327	ribosomal protein L13	ribosomal protein L13
635	1586	X78848	glutathione S-transferase, alpha 1	glutathione S-transferase, alpha 1
13940	1587	X79321	microtubule-associated protein tau	microtubule-associated protein tau
466	1588	X81395	carboxylesterase 1	carboxylesterase 1
570	1590	X82445	nuclear distribution gene C homolog (Aspergillus)	nuclear distribution gene C homolog (Aspergillus)
11849	1593	X93352	ribosomal protein L10a	ribosomal protein L10a
18107	1594	X94242	ribosomal protein L14	ribosomal protein L14
25770	1595	X96437		
14347	1597	Y00156	UDP-glucuronosyltransferase 2B3 precursor, microsomal	UDP-glucuronosyltransferase 2B3 precursor, microsomal
4594	1599	Y07704	Best5 protein	Best5 protein
20173	1605	Z11932	arginine vasopressin receptor 2	arginine vasopressin receptor 2
407	1606	Z11995	low density lipoprotein receptor-related protein associated protein 1	low density lipoprotein receptor-related protein associated protein 1
439	1609	Z22607	Bone morphogenetic protein 4	Bone morphogenetic protein 4
8663	1611	Z27118	heat shock 70kD protein 1A	heat shock 70kD protein 1A
17227	1612	Z36980	D-dopachrome tautomerase	D-dopachrome tautomerase
17226	1612	Z36980	D-dopachrome tautomerase	D-dopachrome tautomerase
1542	1614	Z50144	kynurenine aminotransferase 2	kynurenine aminotransferase 2
8664	1615	Z75029		R.norvegicus hsp70.2 mRNA for heat shock protein 70
15569	1616	Z78279	collagen, type 1, alpha 1	collagen, type 1, alpha 1

Table 2 Atty Ref: 44921-5133-WO	
GI GC Identifier	PLS_Score
25024	-0.03408754
21011	0.005158207
8317	0.00286913
15861	0.01758436
15862	0.01155703
15028	-0.04786289
15154	0.01881327
15296	0.00676223
16518	0.02598835
17764	-0.02342505
20711	-0.01317801
23778	0.002304377
20795	0.00146821
20817	0.0314257
20833	-0.004259089
20919	-0.0198629
20920	-0.007400703
21012	-0.003223273
22351	-0.008960611
15848	-0.01718595
15849	-0.04416249
15850	-0.01030871
23837	-0.0118801
4312	0.003691487
20864	0.007678122
10241	0.01076413
11434	0.06352768
20801	-0.01583562
15126	-0.002417698
15297	-0.006103148
15124	0.01198701
16080	0.02010419
21013	-0.001557214
13479	-0.03089779
13480	0.003500852
6780	-0.003917337
18989	0.000967733
1475	0.01773045
1321	-0.03506051
11955	0.02492273
1920	0.01128843
15189	-0.005276864
17765	-0.02927309
4010	0.0263635
23225	0.01153367
11956	-0.009530467
11755	-0.03076732
20713	0.02154138
25057	0.01553224
17378	-0.008536189
14956	0.00635737
14957	-0.008478985

Table 2 Atty. Ref. 44921-5133-WO	
GLGC Identifier	PLS Score
16468	0.01178596
5733	0.01442401
4748	0.00604811
4749	-0.001180088
17758	-0.01322739
1301	-0.03655559
15125	-0.005030922
17541	0.01180132
6406	0.008492458
1598	0.03642105
17805	-0.01636465
1537	-0.02368897
16768	0.005025752
17158	-0.006618596
1037	-0.03482728
17377	0.009030169
8664	0.005364025
15569	-0.01163379
15408	-0.004117654
15409	0.02009719
4615	-0.0216485
16148	-0.007715343
21078	-0.002250057
23109	0.005140497
25064	-0.02576101
1466	-0.0115101
15741	0.001858723
13723	-0.03098842
1183	0.007847724
1174	-0.02682282
1814	-0.02409571
23445	0.01268358
25069	-0.01803054
25070	-0.001117053
1247	0.002905345
17301	0.02169327
14346	0.01814763
15017	-0.005796293
634	0.02392324
17806	-0.03059827
15174	0.02558445
20887	0.003184597
20818	0.03540093
33	0.000687164
23523	0.04827108
1853	0.000184702
23987	-0.009158069
21651	-0.01072442
635	0.01430005
14347	0.007348958
25098	0.01413377
17157	0.002967211

Table 2 Atty Ref 44921-5133-WO	
GLGC Identifier	PLS Score
17337	0.03499423
15703	0.003194804
15662	-0.01996508
13973	0.01031566
18075	0.001804553
18076	0.01474427
4234	-0.03231172
23625	0.008422249
15243	-0.009537201
25165	0.004905388
3454	-0.01269925
23045	-0.01042821
17326	-0.01356372
17327	-0.01550095
22603	0.01994649
117	-0.01073836
16649	-0.003848922
985	-0.004571139
4011	0.02594932
16007	-0.03245922
16155	-0.03767058
25198	-0.04053008
744	0.01448024
5496	-1.62254E-05
5497	-0.004547023
25204	0.01864999
17535	0.01886001
16156	-0.01055435
4723	-0.02257333
2367	0.00281055
2368	0.0198073
6554	-0.01628744
12422	-0.003597185
12423	-0.01363361
25247	0.02928529
20404	-0.003382577
18956	-0.03746372
2554	0.001275564
3254	-0.02432042
4003	-0.01871112
25257	-0.006161937
15281	-0.02035118
1214	0.01756383
18727	-0.01572102
18246	0.001154571
18452	-0.01337099
18453	-0.007857254
20493	0.01936436
5492	-0.01191286
18028	-0.03629819
1354	0.009908063
25290	0.02397325

Table 2 Atty Ref 4492-5133-WO	
GLGC Identifier	PLS Score
20494	-0.000954101
18750	-0.02634051
25315	-0.03588133
3987	0.009837479
20149	-0.04258657
22412	-0.004335643
22413	-0.00221225
109	-0.005122522
22411	0.01450058
455	-0.01210526
25405	0.01309029
20298	-0.05332408
1622	-0.003529147
21882	0.006960723
7872	-0.01691339
24615	-0.003635782
25460	-0.007971963
25467	-0.002433017
25468	0.009742874
25469	-0.01432337
16449	-0.000927568
16450	0.004114473
5837	-0.005018729
25480	0.006534462
25481	0.03633816
4012	0.02058364
10886	-0.02500923
5493	-0.00559364
15127	0.01913647
14003	0.00302135
355	0.001723895
356	-0.01191485
16248	0.02829451
15832	-0.003373712
1471	-0.007821926
18647	-0.00834588
25518	-0.01890072
9224	-0.009229792
15135	0.03026445
25525	0.01468858
18990	0.002379164
16211	-0.01861134
1943	0.01443373
25545	-0.02041409
21583	-0.000591347
25546	-0.006230616
10260	-0.002039004
25563	-0.009749564
14121	-0.01940992
3609	0.0020902
18005	-0.000341325
16268	-0.05654464

Table 2 Atty. Ref. 44921-5133-WO	
GLGC Identifier	PLS Score
22196	0.01060633
12014	0.006231096
16708	0.01482556
16398	0.006464105
25632	0.03466999
4957	0.008092677
25643	-0.03402377
23300	0.03958223
1546	0.01170207
22675	-0.008282468
818	-0.01053171
1550	0.01494726
1551	0.02599436
20715	0.01030098
16947	0.02858744
20884	-0.02730658
24778	-0.02842167
25675	-0.0203886
20810	-0.02795083
15653	-0.00909295
25676	-0.04245567
19244	0.01925244
1069	0.02009015
3202	0.01047109
25682	-0.03644181
25686	0.01175157
20872	0.005200382
15201	0.01743058
9620	0.009678062
20427	-0.007203343
25691	-0.01287446
25699	-0.01975985
10860	-0.01890404
10267	-0.01660402
5667	0.003279787
18611	-0.01685318
17175	0.008473313
25702	0.006244145
10109	0.005310704
25707	0.03233485
15875	0.002634939
25719	-0.01698852
4441	0.01366032
13646	0.01512804
23708	0.000573755
20844	-0.00279304
22219	0.003093927
16272	-0.004407614
25770	-0.01879616
20173	-0.007049952
407	0.004526638
8663	0.01127171

Table 2 Atty Ref: 44921-5133-WO	
GLGC Identifier	PLS Score
19824	1.61079E-05
1921	0.006592317
24428	0.01721819
24438	-0.00262423
18619	0.005152837
24496	-0.03948592
24567	-0.01201788
291	-0.02495906
24770	-0.008714317
24843	-0.03153809
24874	0.02920487
18686	0.01941361
43	-0.01441405
133	0.04627691
24590	-0.01762193
16675	0.03559083
13682	0.003206818
417	-0.0215943
18008	0.003835681
466	-0.003738717
24639	-0.01283457
556	-0.004202022
714	0.005186919
729	-0.003318912
770	0.01406266
797	0.01683459
912	-0.01437363
1928	-0.007305755
1929	0.01778287
16610	0.01123602
24648	0.004198686
1104	0.02800208
1602	0.01814398
8426	-0.0182353
1203	-0.0288901
617	-0.008825291
11692	0.02179052
19997	0.002543063
10071	-0.01549941
16676	0.0117799
19952	0.004150428
15379	-0.02876546
25907	0.03277824
19002	-0.01186146
19943	0.000162394
20082	0.02651264
18078	0.000639759
20839	-0.000873427
4259	0.01316487
15385	0.01291856
4242	0.01189998
16435	-0.000204926

Table 2 Atty Ref. 44921-5133-WO	
GLGC Identifier	PLS Score
16849	0.02508564
15022	0.02776678
8888	0.01160653
1867	-0.00064856
24329	-0.03123893
1729	-0.03759896
9541	-0.03444796
21696	0.009596217
20812	0.0196699
13938	-0.01164793
15434	-0.006764275
15097	0.001716813
23362	-0.0179409
17473	-0.01096604
15616	0.001493839
18713	0.01234178
815	-0.02093439
15247	0.01110444
21950	0.000306391
21682	-0.006126722
20802	-0.01220903
23709	0.02399753
16510	0.03670125
4449	-0.00546298
18077	0.0171604
17160	0.01415535
2109	-0.005310179
15190	-0.01250142
16918	-0.01725919
23660	-0.01086482
8749	-0.03118036
18687	0.003382211
21975	0.01300874
21842	0.001369081
15191	0.01105956
20717	0.01063375
3431	-0.006921202
17570	0.007088764
15259	-0.01822124
17563	-0.02220618
17829	0.005354438
16081	0.0205121
1474	-0.03084054
17448	0.02467472
9125	-0.01139344
17196	-0.06969452
8212	0.02652411
20702	0.002678285
573	-0.02872789
409	-0.007299354
4574	-0.02958615
754	-0.0157468

Table 2 Atty Ref 44921-5133-WO	
GLGC Identifier	PLS Score
15468	0.000192713
12700	-0.01010274
14124	-0.01342113
20126	0.0146427
4450	-0.04028917
4451	-0.04007754
17197	0.02424782
17198	0.033739
16726	0.01229342
23698	0.01072602
23699	0.005510382
1540	0.02953147
19255	-0.02175437
19256	-0.047948
20405	0.02330483
20885	-0.003796437
46	0.01204979
6055	-0.01505172
14997	-0.01111345
24563	0.002454691
24564	-0.01268496
24651	-0.0234343
240	-0.01207596
10878	-0.05290645
17105	0.02110802
1514	0.007158728
15112	-0.007915743
24900	0.000776591
9109	0.02180698
1427	-0.01731983
16683	-0.02202782
3549	-0.002275369
23524	0.02175325
19825	0.001300221
18958	-0.009980402
20803	-0.01980488
16871	-0.02941303
12606	-0.006382196
1970	-0.00636348
23826	-0.001208646
20925	0.01287874
20780	-0.009828659
16895	-0.01042923
1424	0.01814117
20481	-2.73489E-05
1542	0.01467805
17226	0.04658792
17227	0.03661337
1479	-0.02727375
1558	0.001784993
1559	-0.00440292
20753	0.000428273

Table 2 Atty Ref. 44921-5133 WO	
GLGC Identifier	PLS Score
20865	-0.02611805
1306	0.01473606
19543	0.01029956
15872	0.006396827
24640	0.02250593
20597	-0.0072339
439	0.002488504
20518	-0.008984546
12903	0.007889638
21562	0.002491812
10248	0.03579842
23606	-0.000202168
21122	0.005247012
21123	0.01623291
570	0.0196455
16847	0.01145459
16204	0.02414009
16205	0.008361849
23854	-0.01483347
24626	-0.0146705
1885	-0.01965638
13940	0.000886116
18108	-0.005199345
646	-0.05841963
20513	0.02871836
20483	0.002659336
11849	0.01031365
1977	0.000325571
20772	0.01157497
16448	-0.01863292
18107	0.0166564
755	-0.03462439
16681	0.0152882
4198	0.02822708
4199	0.004798302
16147	0.01038541
17554	-0.02472233
16354	0.02817476
945	0.00993543
989	-0.01391793
16407	-0.000955995
7914	0.000102491
1419	-0.04516254
24885	0.01988852
7064	-0.005395484
17149	0.02755652
17150	0.03952128
17393	-0.005221711
17394	-0.00579925
1508	-0.0102906
17284	-0.007007458
17285	0.0214901

Table 2 Atty Ref 44921-5133 WO	
GLGC Identifier	PLS Score
18501	0.02471658
18502	-0.03477159
4589	-0.000894857
18597	0.005855973
4594	-0.01689378
16444	0.02065756
20809	-0.02390898
15411	0.01785927
4467	0.01709855
18070	0.01584395
7488	-0.02057392
24643	-0.001264686
1509	0.00454317
13005	-0.006822573
1894	-0.00274857
4254	-0.01411081
1762	-0.01280683
1763	-0.003490757
7784	0.002189607
23961	-0.005958063
20868	-0.01507699
20869	-0.009079757
20699	0.00043838
20700	-0.004172502
11153	-0.02787509
16948	-0.003215995
1678	0.000367942
1976	0.01736856
17502	0.01984278
17661	-0.008856236
15580	-0.02737185
17411	-0.004684325
4178	0.00538893
15150	-0.007069793
11852	-0.000403569
4809	-0.03041049
19067	-0.007720506
20582	-0.04267649
22374	-0.01256255
22927	-0.03448938
4222	-0.0165522
7090	-0.02020823
15927	6.41932E-05
11865	-0.006393904
19402	-0.04323217
16139	-0.009440685
6451	0.006511471
16419	-0.01146098
18084	-0.01723762
15371	-0.01097884
15376	-0.008551695
15887	-0.0465706

Table 2 Atty Ref: 44921-5133-WO	
GLGC Identifier	PLS Score
15888	-0.007077734
15401	0.03108703
18902	-0.003807752
15505	0.02092673
6153	0.005509851
4361	-0.000569115
4386	0.02562726
24235	0.000464768
9952	-0.009126578
9071	-0.000939401
474	-0.01146703
9091	-0.0287723
17420	0.002994313
11959	0.01476976
17693	0.01033417
17289	-0.003851629
17290	0.01185756
20522	0.000628409
20523	0.003173917
17249	-0.02066336
16023	0.006094849
17779	-0.000918023
1159	0.01132209
17630	0.009499276
13420	0.005331431
14595	0.02173968
16529	-0.0408304
4482	0.03541986
4484	0.02414248
18190	0.02839109
17717	0.01780007
9027	0.01143368
13647	0.001145029
820	-0.02052028
12016	0.004811067
21695	0.005617932
4499	0.00030477
8599	0.01191982
12275	0.004126427
12276	0.006840609
18274	0.000625962
18275	-0.006242172
4512	0.01254979
15876	0.0076095
17500	-0.02208598
23783	-0.003488245
13542	-0.001915889
22539	0.006842911
23322	-0.002697228
12848	-0.01525511
3853	0.02945047
3439	-0.01804814

Table 2 Atty Ref 4492.1-5133 WO	
GLGC Identifier	PLS Score
12020	0.01677873
3870	0.007775934
548	0.01829203
17752	0.01777645
18967	-0.03837527
7505	0.00383637
9084	-0.02018928
10540	0.02506434
3895	-0.01868215
18396	0.01085198
18291	0.01498073
23063	-0.002563515
18361	0.01949046
14309	0.002836866
21007	-0.003881654
23203	0.001480229
4412	0.01905504
21035	-0.01397706
18462	-0.0280539
22386	0.01780035